THE
BRITISH JOURNAL OF SURGERY

VOL. XLV SEPTEMBER, 1957 No. 190

RIGHT HEPATIC LOBECTOMY

OPERATIVE TECHNIQUE, SOME ANATOMICAL POINTS, AND AN ACCOUNT OF A CASE

BY O. V. LLOYD-DAVIES AND J. C. ANGELL, LONDON

THE removal of portions of the liver is now quite a frequent occurrence. The majority of cases reported are either local excisions of the wedge type for primary or secondary tumours, or excisions of tumours of the colon, stomach, or gall-bladder which have spread by direct continuity into the liver substance.

Left hepatic lobectomy has been done on many occasions (Lloyd-Davies, 1947; Raven, 1949; Brunschwig, 1953), but in many of the accounts of the removal of the physiological and true anatomical left lobe the description of the plane of section through the liver is not clear. Removal of the so-called left lobe, that is, the portion to the left of the falciform ligament, is not a particularly formidable task. However, Froehlich of Strasbourg (1953) describes very accurately a true anatomical left hepatic lobectomy.

Formal removal of the true anatomical and physiological right half of the liver has been much less frequently attempted, but Lortat-Jacob and Robert (1952) describe a method with a successful case.

In January, 1954, we operated on a man aged 39 for carcinoma of the mid-pelvic colon. At that operation a large single secondary deposit, about the size of two fists, was found in the right lobe of the liver. The size of the deposit, and its singularity, suggested that an embolic metastasis had taken root in the liver early in the course of the disease, and since no other metastases could be felt it was hoped that it was the only one.

A classical wide resection of the primary tumour was performed, ligating the inferior mesenteric artery at its origin from the aorta and the vein at the inferior border of the pancreas. The para-aortic tissues and mesenteric field were cleared and the whole pelvic and iliac colon resected, continuity being restored by mobilizing the transverse colon and splenic flexure and anastomosing the region of the splenic flexure to the rectum.

The pathological report revealed the primary tumour to be an adenocarcinoma of an average grade of malignancy, with slight local spread and five lymphatic-gland metastases. Fortunately the five involved glands were closely related to the bowel wall (pericolic), and the remaining extensive lymphatic field which had been removed showed no evidence of spread.

It was therefore felt that the patient had a reasonable prognosis except for the presence of the hepatic metastasis, and that removal of the right lobe of his liver was a risk worth taking, there being no clinical or radiological evidence of spread elsewhere.

It was desired to devise an orderly technique which would be safe for the patient, without gross loss of blood, if successfully accomplished, and which would allow a retreat from the field without having taken an irrevocable step, should insuperable difficulties be met with at any stage.

A study was made of a number of subjects in the post-mortem room, where invaluable information was gained. The operation, performed on Feb. 26, 1954, was based entirely on these experiences.

ANATOMICAL CONSIDERATIONS

The Hepatic Veins.—Dissection of livers in the post-mortem room reveals a wide variation among the terminal hepatic veins at their junction with the inferior vena cava.

There are always a large right and a smaller left hepatic vein draining the corresponding lobes and occasionally they are the only veins doing so (*Fig.* 129 a). The variations are in the main the result of the rather capricious behaviour of a third central vein. This varies both in its field of drainage and in its relation to the right and left hepatic veins.

1. It may drain the left part of the right lobe and enter the inferior vena cava separately between the right and left hepatic veins at a slightly lower level (*Fig.* 129 b).

2. It may drain from the left lobe in addition to the left hepatic vein, which it joins just before or at its point of entry into the inferior vena cava (*Fig.* 129 c). In such a case the central vein is in effect the chief pathway of venous return from the left lobe and must remain intact if the left lobe is to survive, the left hepatic vein being merely a subsidiary vessel and smaller than usual. But in addition, and this is a practical point, the central vein frequently has a large tributary from the right lobe which joins it just before it leaves the liver substance (*Fig.* 129 d). When this is so, section of

the liver between right and left lobes would result in considerable hæmorrhage from the cut surface, as of course the central vein must not be ligated outside the liver.

3. The central vein may drain mostly from the right lobe and join the right hepatic vein just before or at its junction with the inferior vena cava, having only a small tributary from the left lobe, which is

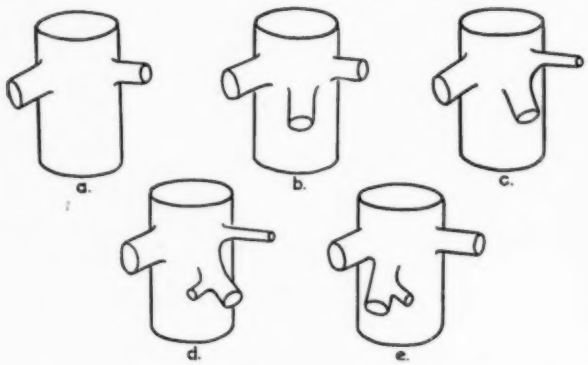


FIG. 129.—Diagrammatic representation of termination of hepatic veins as seen from in front.

presumably unimportant, as the left hepatic vein is normal in size, providing adequate drainage of the left lobe (*Fig.* 129 e).

From the practical point of view it is the relation of the central vein to the left lobe which matters, and fortunately a reliable forecast of this may be made before dissection of the hepatic veins is started.

If the inferior vena cava immediately below the diaphragm is inspected, the right hepatic vein can always be seen as a broad blue structure under cover of the peritoneal reflection, as it passes from the posterosuperior border of the liver to enter the inferior vena cava on its right anterolateral aspect. If the left hepatic can also be seen, passing through the base of the left triangular ligament to enter the left anterolateral aspect of the vena cava at the same level as the right hepatic vein, and appears normal in size (i.e., two-thirds the size of the right hepatic vein), it can be presumed that it is providing adequate drainage for the left lobe. In such circumstances a central vein, if present, may be divided posteriorly without harm. But if a normal sized left hepatic vein cannot be seen in this situation, the presence of a central vein can be predicted and must be left intact, as it will be vital for adequate venous drainage of the left lobe.

In addition to these main hepatic veins there are a variable number of small short veins passing directly from the back of the liver to the inferior vena cava at a lower level. Very rarely one of them may be large, forming an accessory right hepatic vein.

Relation of the Inferior Vena Cava to the Liver.—About 2 cm. below the diaphragm there is a tongue-like process of liver substance, occasionally fibrotic, which wraps round the right side of the vena cava and obscures the approach to the right hepatic vein, and also the central vein if present. It is often quite adherent and needs careful dissection to avoid injury to the great veins (*see Fig.* 132).

The Plane between the Right and Left Lobes.—It is now well known that the anatomical division of the liver into right and left lobes is not in the line of the falciform ligament. The work of McIndoe and Counsellor (1927), Elias and Petty (1952), and others, based on embryological, anatomical, and pathological studies, has shown that the line of division between the lobes passes from the left border of the gall-bladder fossa to the vena cava foramen. This plane is constant and separates the arterial, venous, and biliary systems of each side. The quadrate lobe is part of the left side, as is the left half of the caudate lobe, its right half belonging to the right side of the liver (Couinaud, 1952). The plane of cleavage takes an oblique course from the right side of the quadrate lobe to a point just to the right side of the left hepatic vein as it leaves the liver.

Although some accounts of right hepatic lobectomy describe removal of the caudate lobe, practical observations in the post-mortem room show that an attempt to do so gravely endangers the blood-supply and biliary drainage of the left lobe, and we feel that it should be left intact for safety's sake. In any case, only half the caudate lobe drains into the right side of the liver.

THE OPERATION OF RIGHT HEPATIC LOBECTOMY

The patient was placed on the table in a half-left lateral position, so that by tilting the table, supine or full-left lateral positions could be obtained at will.

The eighth rib was excised, the costal cartilage divided, and the incision continued as a right paramedian to the level of the umbilicus. The diaphragm was divided from the incised costal margin to the vena cava foramen. This gave adequate exposure and with the patient supine allowed the liver to fall into the chest, enhancing the view of the portal fissure.

The first step was the dissection of the porta hepatis to display the vessels and ducts entering the liver, with the exception of the branches of the portal vein, which were still hidden by the right hepatic artery and duct (*Fig.* 130). The cystic duct and vessels were divided. The right hepatic duct and artery were isolated, but not divided, as this would have constituted a point of no return before it was certain that the operation was possible, which of course was dependent on the successful dissection and division of the right hepatic vein. Tapes were passed around the inferior vena cava above the renal veins and above the diaphragm, to minimize blood-loss should the main veins be damaged.

The patient was then tilted into the left lateral position to allow the liver to fall to that side, and the right triangular ligament, together with the anterior and posterior layers of the coronary ligament, was divided, thus completely freeing the right lobe of the liver from the diaphragm. Minor bleeding from the bare area was readily controlled by diathermy. At this stage, with the patient supine, the hepatic veins were examined and fortunately a normal-sized left hepatic vein was visible (*Fig.* 131).

With the patient again in the left lateral position the right lobe was drawn to the left, exposing the vena cava in its fossa, and displaying the short hepatic veins, which were just long enough to divide between ligatures passed on a fine aneurysm needle. They were divided from below upwards, and the tongue

of liver passing behind the right edge of the vena cava was freed (*Fig.* 132). The inferior border of the right hepatic vein was then visible and blunt artery forceps were passed from below along its medial side, to emerge above the liver to the right of the left hepatic vein (*Fig.* 133). A ligature was

FIG. 130.—Dissection of portal fissure, drawn from case described. Note how right hepatic artery and duct obscure terminal branches of portal vein.

FIG. 131.—View of hepatic veins over superior surface of liver. Note normal-sized left hepatic vein, indicating that a central vein, if present, is unimportant.

FIG. 132.—Forceps passed around partly fibrous tongue of liver which embraces the inferior vena cava. It must be divided to expose the right hepatic vein.

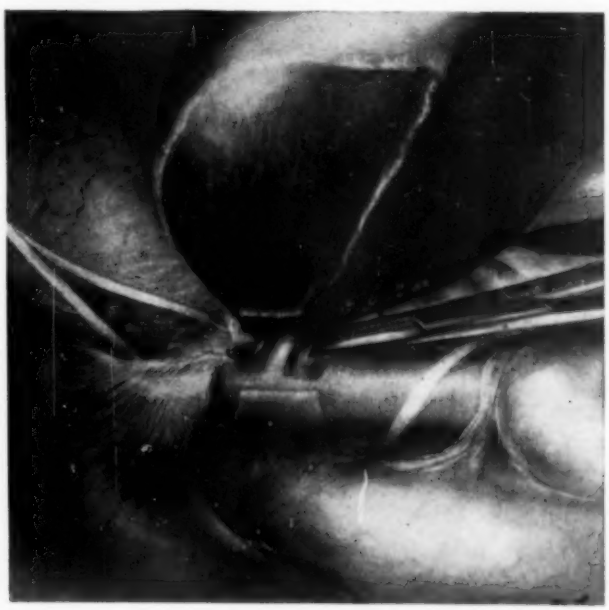


FIG. 133.—Forceps passed between right and left hepatic veins to withdraw ligature. Note divided tongue of liver and ligated minor hepatic veins.

withdrawn and tied flush with the vena cava. There was not room for a second ligature, and the distal part of the vein was clamped in the liver substance before dividing it. This was the most precarious part of the operation, but its safe accomplishment made the operation feasible. In this case there was no central vein. The tapes around the vena cava were then removed.

The patient was turned supine and the liver once more allowed to fall into the chest, displaying the porta hepatis. The previously isolated right hepatic artery and duct were divided between ligatures, allowing for the first time a good view of the main branches of the portal vein high in the porta. The gall-bladder was removed to improve the exposure and to display the line of section of the liver. The right branch of the portal vein was ligated, clamped, and divided in a similar manner to the right hepatic

vein, with a clamp on its proximal end embedded in liver substance.

The stage was now set for division of the liver, and this was done with a scalpel in the plane described, only a few small vessels being encountered, which could be seized with forceps and tied. The cut surface was compressed with mattress sutures of catgut and as much as possible covered with peritoneum, obtained by reflecting the lower parts of the falciform and round ligaments.

As a completely accurate section of the liver could not be guaranteed, some leakage of bile from the cut surface, particularly the caudate lobe, was anticipated. To minimize this a T-tube was placed in the common hepatic duct.

A large corrugated drain was placed under the repaired diaphragm and the wounds closed with a negative-pressure drain in the pleural cavity.

The blood-loss was relatively small, the patient receiving a litre and a half of transfused blood during the operation.

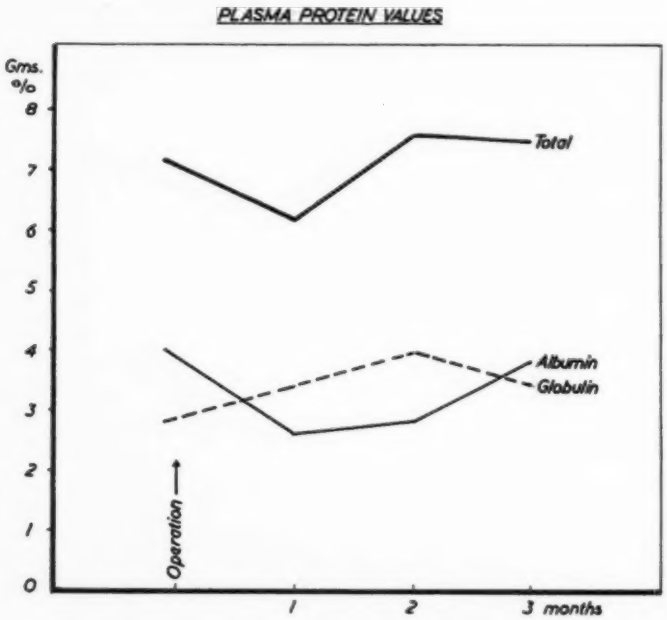
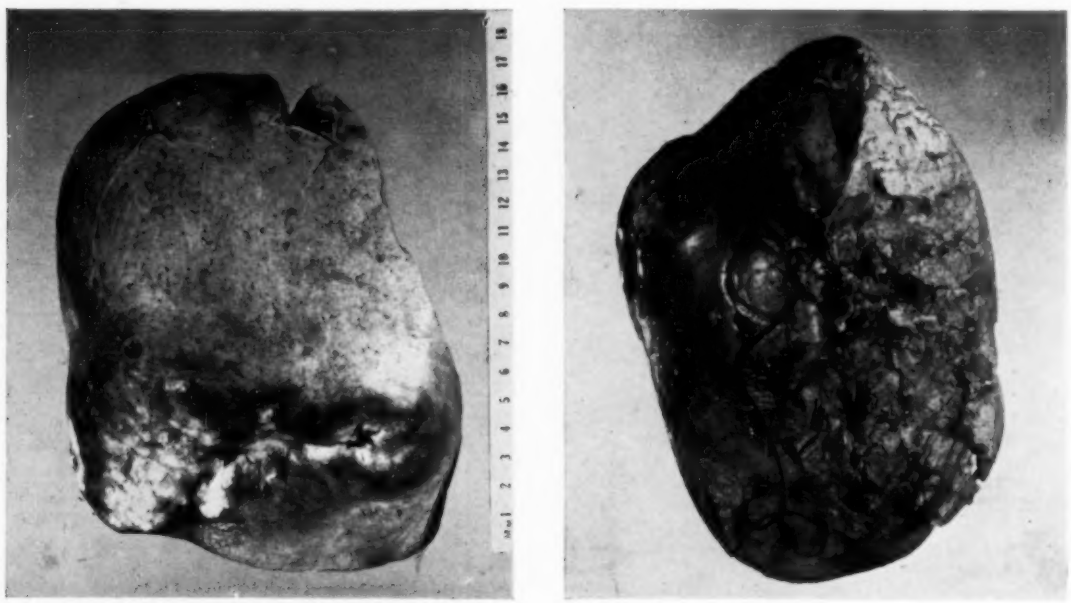


FIG. 134.—Change in serum protein levels following operation.

POST-OPERATIVE PROGRESS

The patient's general condition was never a cause of anxiety, the temperature and pulse-rate reaching a normal level by the fourth day. Normal peristalsis was established on the second day and intravenous fluid administration stopped. He was out of bed on the fifth day. The lung had fully re-expanded the day following operation and the intrapleural drain was removed; no subsequent aspiration was necessary. Antibiotics and vitamin K were administered for eight days.

Biliary Drainage.—The daily quantity of bile draining from the T-tube in the common hepatic duct was less than 2 oz. for the first three days, after which it gradually increased, though never exceeding 16 oz. In addition, a considerable amount of bile-stained serum drained from the cut edge of the liver along the corrugated drain.



A B

FIG. 135.—The resected right lobe. A, Anterosuperior view. B, Inferoposterior view, showing cut surface. Note stump of right hepatic vein at lower end of picture to the right of the looped ligature which is on the right hepatic artery.

On the second day jaundice was noted. This increased in intensity until the fourth day and then declined, disappearing by the sixth day. The assurance of normal biliary drainage given by the presence of the T-tube, especially during the period of jaundice, was a great comfort and its insertion was considered justifiable from this point of view

alone. The jaundice was never severe, the serum bilirubin measuring 4·2 mg./100 ml. at its height. It was thought to be due to biliary absorption from the dead space.

Drainage of bile-stained fluid from the cut edge of the liver gradually lessened after ten days and was absent on the twelfth, but spigoting of the T-tube was promptly followed by a profuse recurrence. It was therefore allowed to drain freely for a further twelve days and finally removed on the thirtieth post-operative day. Meanwhile on the fourteenth day the corrugated drain had been replaced by a fine catheter, to allow some contraction of the track.

The Liver Dead Space.—The dead space drained by the catheter was slow to close in spite of irrigations, deep-breathing exercises, and some attempt at postural persuasion by having the patient lie on his right side with the foot of the bed raised for long periods.

He went home on the thirty-eighth day with the catheter, now shortened, still in place. Regular sinograms were taken and the catheter shortened, but it was not finally removed until seven months after operation. As late as the sixth month bile pigments were occasionally demonstrable in the discharge from the narrow track leading to the liver.

METABOLISM

Weight.—Three months after operation the patient had regained his pre-operative weight and by the seventh he was as heavy as he had been before he became ill two and a half years previously, having regained 3 stones in all.

Liver Function Tests.—Alkaline phosphatase, thymol turbidity, colloidal gold, bromsulphalein excretion, and cephalin cholesterol values were all normal before hepatic lobectomy and at intervals of one, two, and three months afterwards. Serum bilirubin levels and van den Bergh reactions were normal except during the transitory period of jaundice.

The plasma proteins showed a temporary reversal and are shown in the accompanying graph (*Fig.* 134).

PATHOLOGY

The portion of liver removed weighed 945 g. (*Fig.* 135). It contained a large solitary mass of metastatic adenocarcinoma of an average grade of malignancy.

It is now over two and a half years since the operation and the patient remains in excellent health with no sign of recurrence.

SUMMARY

1. A technique for formal removal of the right lobe of the liver with minimal blood-loss is described, together with a successful case.

2. The feasibility of the operation depends on successful ligation of the veins draining the right lobe of the liver. The variations and their surgical significance are described.

3. No irrevocable step need be taken before the success of the operation is assured.

Acknowledgements.—It is a pleasure to acknowledge the co-operation of Professor E. W. Walls, of the Middlesex Hospital Anatomy Department; his special knowledge was of immense help and his clinical interest a great encouragement.

Reassuringly tranquil anæsthesia for both operations was administered by Dr. A. J. H. Hewer.

The nursing of the patient was in the capable hands of Miss Ellen Fletcher.

The drawings are by Miss Hewland and the photographs by Mr. Turney of the Middlesex Hospital Medical Art and Photography Department.

REFERENCES

BRUNSCHWIG, A. (1953), *Cancer*, **6**, 725.
COUINAUD, C. (1952), *J. Chir.*, **68**, 697.
ELIAS, H., and PETTY, D. (1952), *Amer. J. Anat.*, **90**, 59.
FROELICH, F. (1953), *Mém. Acad. Chir.*, **79**, 730.
LLOYD-DAVIES, O. V. (1947), *Proc. R. Soc. Med.*, **40**, 875.
LORTAT-JACOB, J. L., and ROBERT, H. G. (1952), *Pr. Méd.*, **60**, 549.
McINDOE, A. H., and COUNSELLOR, V. (1927), *Arch. Surg., Chicago*, **15**, 589.
RAVEN, R. W. (1949), *Brit. J. Surg.*, **36**, 397.

CARCINOID SYNDROME WITH PELLAGROUS DERMATITIS

BY J. M. BRIDGES, J. B. GIBSON, LAVINIA W. LOUGHRIDGE, AND D. A. D. MONTGOMERY

FROM QUEEN'S UNIVERSITY AND THE ROYAL VICTORIA HOSPITAL, BELFAST

THE association of cardiac lesions and carcinoid tumour has been recorded from time to time over the past twenty-five years (Smith and Campbell, 1956), but it was only in 1952 that Biörck, Axen, and Thorson described the clinical syndrome and unified the conception of the disease. Skin and vasomotor changes, asthma, and diarrhœa are now recognized as associated features and the level of 5-hydroxy-indole-acetic acid (5-H.I.A.A.) in the urine is regularly increased in the disease. This biochemical feature makes confirmation of a presumptive clinical diagnosis possible.

The case reported here draws attention to the slow evolution of the cardiac lesions, which were remarkably well developed at the time of death. In the later stages, a pronounced skin rash indistinguishable from pellagrous dermatitis was an important feature of the illness. The results of special investigations on the peripheral circulation are also recorded.

CASE REPORT

The patient, a 60-year-old housewife, was well until June, 1951, when she first noticed painless swelling of the ankles in the evenings. There was no related exertional dyspnœa, and in September she was seen in the Outpatient Clinic by one of us (D. A. D. M.). Direct questioning failed to elicit any history of rheumatic fever, and she had undergone two pregnancies without distress thirty and twenty-six years before.

At this time she presented a healthy appearance despite slight ankle œdema. Auscultation revealed a

mitral diastolic murmur and a systolic murmur of "squeaking" quality at the apex. The blood-pressure was 185/120 in the right arm and 165/100 in the left. The liver was enlarged, but no expansile pulsation or other evidence of tricuspid valve disease was found. The electrocardiogram showed left axis deviation with flat T waves in the precordial leads. Chest screening revealed

FIG. 136.—The legs and feet of the patient to show the reddish-brown discoloration and the stretched and glistening appearance of the skin.

early left ventricular enlargement, and the œsophagus was displaced backwards by a moderately enlarged left auricle. A diagnosis of mitral stenosis with mild arterial hypertension was made, and a régime of salt restriction with diuretics recommended.

She remained well apart from mild dyspnœa on exertion until 1954, when she first developed diarrhœa. This consisted of the passage of up to six unformed bowel motions daily, preceded occasionally by mild abdominal cramps. In February, 1956, the diarrhœa became more severe, persisting unchanged until her admission to hospital in May.

In September, 1955, she first noticed an alteration in the skin of her hands, feet, and legs, which she described as "dry and withered looking". During the summer, the affected areas had been markedly sun-tanned, but the pigmentation had continued to increase during the winter, and the skin had become progressively more dry (*Fig.* 136). She complained of occasional facial flushes, which she described as sudden "hot and tight" sensations, often following a hot drink, or occasionally alcohol, which she rarely consumed. She stated that she had not lost weight and, though weak and occasionally breathless on exertion, had had no attacks resembling asthma.

ON EXAMINATION (May, 1956).—The face showed a reddish-blue discoloration in the distribution of a malar flush, but of a brighter hue than that seen in mitral stenosis. This change was present to a lesser extent over the forehead and nose. The extensor surfaces of the hands and forearms showed marked reddish-brown pigmentation with hyperkeratosis and scaling. Patchy areas of cyanosis on the palms contrasted with a bright red colour on the finger tips. There was no finger clubbing. The lower limbs had a striking appearance (*Fig.* 136); from the knees to the ankles, sharply demarcated above, the skin was red-brown in colour, glistening, and tightly stretched over the underlying tissues which pitted readily on pressure. The further finding of dark brown pigmentation on the dorsum of the feet and toes, with fine scaling, completed the picture first diagnosed as pellagrous dermatitis. There was no abnormality of the buccal mucosa, however, and no glossitis.

Cardiovascular System.—Systolic venous pulsation was clearly visible on both sides of the neck. The heart was enlarged and the first heart-sound accentuated at the apex with a systolic murmur of moderate intensity conducted towards the axilla. The mitral diastolic murmur, recorded in 1951, was audible only inconstantly. A soft systolic murmur could be heard at the left sternal border and was associated with a short diastolic murmur immediately following the second heart sound in that area. In addition, a variable "squeaking" sound, systolic in time, was detected over the lower end of the sternum. There was no accentuation of the second sound at the pulmonary area. The clinical interpretation of these signs was difficult, but in view of the cervical venous pulsation and expansile pulsation of the liver, a diagnosis

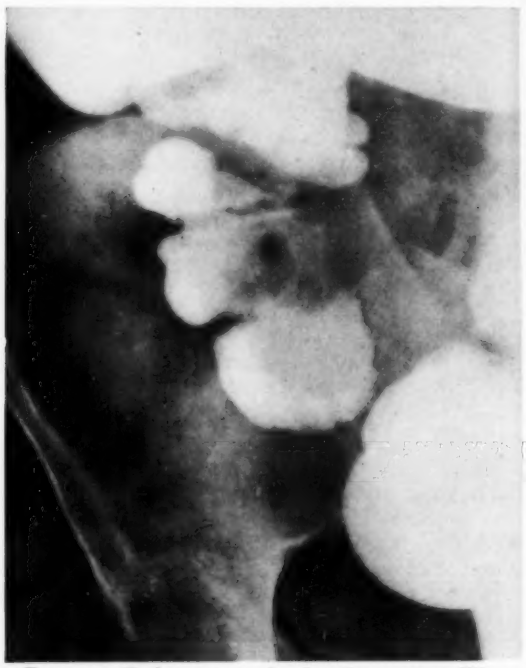


FIG. 137.—Barium enema showing the constant filling deformity in the cæcum.

of tricuspid incompetence and mitral stenosis was made. A firm diagnosis of pulmonary stenosis could not be reached in the absence of the characteristic murmur of that lesion. Systemic blood-pressure varied from 130/90 to 170/100.

Other Systems.—The chest was clear and there was no evidence of bronchospasm at any time. The liver was palpable four finger-breadths below the costal margin with a firm irregular edge and nodular surface. Expansile pulsation was detected. The spleen was considerably enlarged and ascites was present. The patient, although co-operative and intelligent, showed a strange detachment from her environment and seemed unconcerned by the obvious discomforts of diarrhœa, incapacitating œdema, and ascites. There were no abnormal neurological findings.

Radiology.—Barium enema demonstrated a constant deformity in the cæcum suggesting the presence of a neoplasm (*Fig.* 137). Chest screening showed enlargement of both ventricles with marked pulsation of the right cardiac border. The left auricular enlargement, noted in 1951, had persisted, and in addition, there was now expansile pulsation of this chamber.

Liver Function Tests.—Serum bilirubin 2·3 mg. per cent, alkaline phosphatase 12 K.A. units, thymol turbidity 1 unit, zinc sulphate flocculation 9 units; total proteins 6·8 g. per cent, albumin 4·5 g. per cent, globulin 2·3 g. per cent. Prothrombin time was constantly prolonged, the prothrombin index varying between 25 per cent and 45 per cent of normal.

FIG. 138.—The patient during a flush induced by brandy. A brick-red erythema has come up in a few minutes, particularly in the malar region, where a reddish-blue discoloration was present at other times.

Blood.—Hæmoglobin 107 per cent Haldane. W.B.C. 5400/c.mm. (neutrophils 63 per cent, lymphocytes 32 per cent, monocytes 4 per cent). Platelets 178,000/c.mm. Bleeding time 1 min. 30 sec. Clotting time 4 min. E.S.R. 24 mm./1 hr. (Westergren). Serum level of serotonin or 5-hydroxy-tryptamine (5-H.T.) 0·27 μg./ml. (normal 0·1–0·3 μg./ml., Udenfriend, Weissbach, and Clarke, 1955).

Urine.—Urinary excretion of 5-H.I.A.A. was grossly in excess of the normal figure of 5–10 mg./24 hr. (Titus and Udenfriend, 1954), varying between 54 and 272 mg./24 hr. Amino-acid chromatogram of the urine showed no abnormality.

The Electrocardiogram revealed no evidence of right ventricular hypertrophy. T waves in leads aVL and V3–V6 were flat, suggesting a degree of myocardial ischæmia.

The Electro-encephalogram.—Dr. J. H. D. Millar reported as follows: "There is an alpha rhythm at 8 c/s of moderate amplitude and good symmetry. Slow activity at 3–6 c/s, of similar amplitude, is recorded diffusely but is at times more marked in the temporal regions. No focus seen. An abnormal record but no lateralisation seen."

Fæces.—Stool culture—no pathogens isolated. A fat balance revealed no evidence of steatorrhœa.

COURSE AND TREATMENT.—The patient remained in hospital from May 27, 1956, until her death on Aug. 9. Troublesome diarrhœa persisted and her condition deteriorated gradually. She complained of more frequent flushing attacks. During these the skin of her face and hands (both palmar and dorsal aspects) showed first a blotchy-red discoloration, later becoming diffusely purple and reverting to the original cyanotic erythema within 20–30 seconds. On June 27, 4 minutes after the ingestion of ½ oz. of brandy, there appeared a pronounced brick-red erythema of the arms, hands, and to a lesser degree, of the face (*Fig.* 138). The blood-pressures during the experiment were as follows: before alcohol, 170/100 mm. Hg; 3 minutes after, 130/80; 6 minutes after, 150/95. It was also observed on several occasions that firm abdominal pressure resulted in the appearance of a flush.

The exact nature of the cardiac lesion was not ascertained before death, for the murmurs altered in intensity from day to day and the only constant auscultatory finding was the apical systolic murmur. The mitral diastolic murmur, clearly heard in 1951, was inconstant, but the presence of radiological enlargement of the left auricle seemed to confirm the diagnosis of mitral stenosis. Tricuspid incompetence was certainly present, but the source of the fluctuating squeaking murmur was not discovered. The persistently low prothrombin concentration, despite massive treatment with vitamin K preparations, precluded cardiac catheterization to measure pulmonary blood-flows during a flush. This procedure has been carried out on two reported cases of the syndrome (Horsley and Prec, 1956; Goble, Hay, Hudson, and Sandler, 1956).

Treatment with nicotinic acid in daily dosage of 150 mg. resulted in an obvious decrease in the pigmentation and scaling of the skin of the arms and legs. Diarrhœa persisted with increasing severity, however, and despite rigid sodium restrictions, œdema became widespread with gross ascites. As it was felt that surgical treatment of the primary growth was out of the question, it was decided to try the clinical and biochemical effects of a course of chlorpromazine which has been shown, experimentally, to be an antagonist of 5-H.T. (Benditt and Rowley, 1956). The drug was given in 25-mg. doses orally 3 times a day for 14 days. There was no clinical alteration apart from increasing drowsiness, and it was impossible to obtain accurate uncontaminated urine collections for 5-H.I.A.A. estimations. The treatment was therefore abandoned.

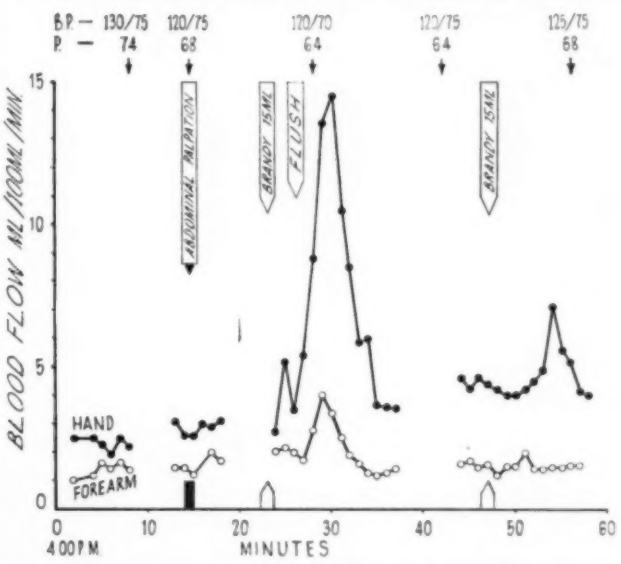


FIG. 139.—Peripheral vascular studies; forearm and hand blood-flow estimations before and after abdominal palpation and the ingestion of brandy.

By this time, ascites had become so severe that therapeutic paracentesis was performed on Aug. 8, following which the patient's condition deteriorated further and she died on Aug. 9.

INVESTIGATION OF THE PERIPHERAL CIRCULATION.—Studies on the peripheral blood-flow (*Fig.* 139) were carried out by Dr. R. F. Whelan and Dr. G. C. Patterson, forearm and hand flows being measured by the method of venous occlusion plethysmography. Resting levels were within

normal limits. At the initial observation, abdominal palpation produced neither flushing nor significant change in the circulation. Subsequently, ½ oz. of brandy by mouth produced a fivefold increase in hand blood-flow and a twofold increase in forearm flow. A second dose, 24 minutes later, produced similar, though less marked effects. It is not known whether these changes were due to a direct effect of alcohol or to a release of 5-H.T. While the effect of intravenous 5-H.T. on forearm and hand circulation is as yet unknown, the fact that intra-arterial 5-H.T. causes a fall in hand, and only a transient increase in forearm flow (Roddie, Shepherd, and Whelan, 1955) suggests that the changes observed could be attributed to alcohol rather than to 5-H.T. release. Alcohol is known to increase the skin blood-flow in the digits, as in the present observations. In order to ascertain the cause of the flush and the increase in peripheral circulation, it was proposed to repeat the experiment, carrying out assays of venous blood for 5-H.T. content, but the patient's death prevented the completion of this investigation.

FIG. 140.—The primary carcinoid tumour is seen as a small ulcerated elevation near the ileocæcal valve in the centre of the picture. The gangrenous cæcum which had perforated is seen on the left below. (× 0·45.)

FIG. 142.—The ventricles of the heart from below. The stenosed pulmonary valve is seen above and the infundibulum is propped open. The endocardium is thick and porcelain-like in much of the right ventricle, in contrast to the normal endocardium of the left ventricle. The right side of the heart is dilated and the myocardium hypertrophied. (× 0·17.)

AUTOPSY FINDINGS.—At autopsy, the peritoneal cavity was the seat of fibrino-purulent peritonitis due to a recent rupture of the cæcal wall which was partially gangrenous (*Fig.* 140). In the wall of the ileum 2 cm. from the ileocæcal valve was a greyish tumour, 1·5 cm. in diameter, over which the mucosa was raised and ulcerated (*Fig.* 140). It had infiltrated through the wall and invaded the adjacent lymph-nodes. Extensive secondary deposits, of pale buff colour and markedly hæmorrhagic, were present in the liver (3000 g.) (*Fig.* 141) and occluded the main right hepatic vein. The retropancreatic and para-aortic nodes were also replaced by tumour deposits.

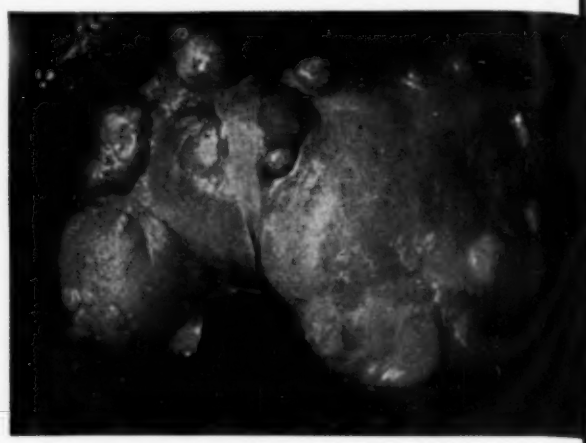


FIG. 141.—Anterior surface of the liver enlarged by many nodular secondaries. (× 0·06.)

FIG. 143.—The stenosed and incompetent pulmonary valve seen from above. The ascending aorta is on the left. (× 0·26.)

The heart (420 g.) showed considerable right-sided enlargement (*Fig.* 142). The right auricle was dilated and the endocardium greatly thickened. The tricuspid valve, which admitted only two fingers, showed fusion and thickening of the cusps. The right ventricle was moderately dilated; the myocardium was 9 mm. thick and of an even colour and consistency. The endocardium on the lateral and apical walls was greatly in excess of normal and had an appearance like porcelain (*Fig.* 142). The tip of the little finger only could be passed through the pulmonary valve; the cusps were altered into firm rounded cushions and were fused to form a small stenotic and incompetent orifice (*Fig.* 143). The chambers of the left side of the heart were unaffected. The mitral valve was of normal calibre, but the cusps were slightly thickened along the line of closure. The left ventricular muscle was 15 mm. thick. The aortic valve was normal and the coronary arteries were free of atheroma.

Histologically the *tumour* in the ileum was an argentaffin carcinoma consisting of solid clumps of rather small cells with poorly defined borders and prominent nuclei (*Fig.* 144). There was a marked fibrous tissue reaction in the

deeper layers of the wall, and the tumour had permeated the perineural lymphatics. The deposits in the liver and lymph-nodes were generally similar, but in the liver a few distinct glandular acini were present. The right ovary contained a microscopical tumour deposit. Only a few argentaffin granules, in widely scattered areas, were revealed on staining by Masson's method. Sections were studied from many parts of all *cardiac chambers*. The increase in endocardial tissue of the right auricle and ventricle was due to formation of dense acellular fibrous tissue, possibly by the organization of mural thrombus, although this process was not demonstrated. The myocardium was not abnormal, but a few of the small vessels in the right ventricle showed some intimal thickening. There was no evidence of rheumatic disease. In pigmented *skin* from the leg the basal layer of the epidermis contained excessive melanin. Acanthosis, atrophy of the skin appendages, œdema, and a little chronic inflammatory infiltrate were present, as they are in pellagra, but in this case there was much greater vascularity of the dermis.

DISCUSSION

The clinical diagnosis was made here in view of bizarre skin changes, long-standing diarrhœa, and cardiac murmurs of uncertain significance, for these can result directly or indirectly from excessive production of 5-H.T. Liver enlargement indicated that metastases of sufficient size were present to produce this excess. The diagnosis of mitral stenosis made in 1951 was not confirmed at autopsy and the murmurs heard then resulted from changes in the function and not in the structure of the heart. Although it is probable that this early disorder of function was due to the production of 5-H.T. by the carcinoid tumour, the patient's condition remained remarkably good for three years afterwards till diarrhœa began. Murmurs of functional type have been recorded in cases in which valvular and endocardial lesions were absent at autopsy (e.g., Jenkins and Butcher, 1955, *Case* 1), and such murmurs apparently precede the formation of cardiac lesions. Increased pulmonary blood-flow is known, in some instances, to be associated with a functional diastolic murmur, and an enlargement of the left auricle and an early increase in pulmonary blood-flow may have been the cause of these findings in our patient in 1951. The murmur was no longer so plainly or constantly audible by the time of her last admission, when pulmonary stenosis had developed. Similarly, the fluctuating quality of the cardiac murmurs during the later stages of her illness may have been related to temporary variations in the serum level of 5-H.T. with resultant changes in cardiac hæmodynamics. Thorson, Biörck, Björkman, and Waldenström (1954) described a patient whose heart-sounds were normal, but who developed an apical presystolic and systolic murmur during an obvious flushing attack at a time when the serum level of 5-H.T. was probably increased. This alteration in the quality and intensity of murmurs in the carcinoid syndrome may afford a valuable clue in reaching a diagnosis in an otherwise obscure cardiac lesion.

At the time of the patient's admission to hospital in May, 1956, the association of pellagra with a strange *mental state* suggested the diagnostic possibility of "H-disease", a genetically determined condition, described by Baron, Dent, Harris, Hart, and Jepson (1956). This syndrome comprises pellagrous skin changes, intermittent cerebellar ataxia, mental deterioration, a constant and diagnostic renal amino-aciduria (Evered, 1956), and excretion of indole derivatives, including tryptophane (Jepson, 1955). In our patient, the cerebral disturbance consisted of a degree of euphoria, despite her incapacitating symptoms, together with an unusual detachment from her surroundings in hospital. There were, however, no neurological signs, and the urinary amino-acid chromatogram was normal. Mental

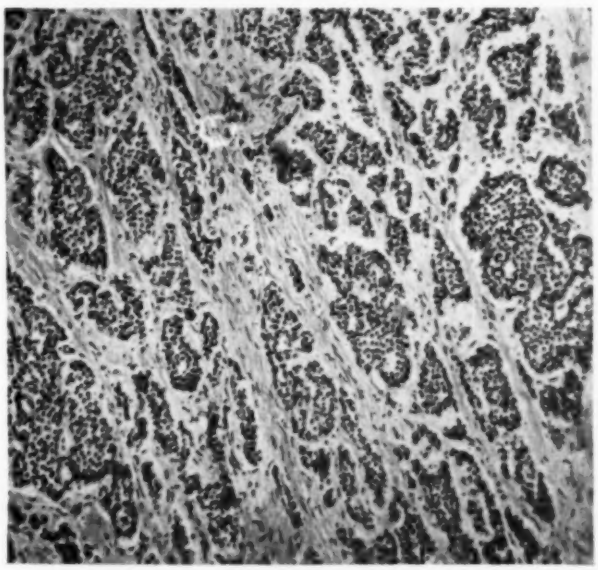


FIG. 144.—The carcinoid tumour in the ileum. It is composed of clumps of well-differentiated cells with prominent nuclei. There is a moderate amount of stroma in the tumour in this site. (× 75.)

disturbance had been described previously in the carcinoid syndrome, however, and experimental evidence suggests that this may be a direct effect of serotonin (5-H.T.) accumulation (Woolley and Shaw, 1954; Feldberg and Sherwood, 1954). Previous authors have commented on a *skin rash* resembling that of dietary pellagra in carcinoid tumours with hepatic metastases (McNeely and Jones, 1946; Biörck and others, 1952; Thorson and others, 1954). Recently, Sjoerdsma, Weissbach, and Udenfriend (1956) have shown that much of the dietary tryptophane is diverted in this disease from its normal metabolic pathway and is utilized as a precursor of serotonin, thus inducing a relative deficiency of niacin. They found that normally only about 1 per cent of dietary tryptophane is utilized in the 5-hydroxy-indole pathway to compounds of serotonin type, leaving adequate tryptophane for formation of niacin and protein. In the carcinoid syndrome, however, up to 60 per cent of the tryptophane intake may be used by the tumour, resulting in the clinical features of niacin and protein deficiency, particularly where there is associated diarrhœa. Daily supplements of 150 mg. of nicotinic acid given to our patient caused considerable reduction in the pigmentation and scaling of the skin, a more marked improvement than is common, we believe, in attempts to correct true dietary pellagra. Diarrhœa, on the other hand, continued unchecked. Probably the increased gut motility is

a direct effect of serotonin release rather than a feature of niacin deficiency, since it has been noted following serotonin administration in the anæsthetized dog and rabbit (Freyburger, Graham, Rapport, Seay, Govier, Swoap, and Van der Brook, 1952).

The clinical reproduction of spontaneously occurring flushes in the patient, following abdominal palpation and alcohol ingestion, led to detailed blood-flow studies (*see Fig.* 139). It seems likely, however, that the increased blood-flow observed resulted from a potentiated but direct alcohol effect rather than from secondary 5-H.T. release from the tumour, although this interpretation was not checked by blood-assays. It is unfortunate that abdominal compression, on this occasion, did not produce the characteristic response to enable peripheral blood-flows to be recorded. It is possible that at the times when this manœuvre did induce a flush, additional amounts of 5-H.T. were released into the blood-stream either from the ileal tumour or from its hepatic metastases. Dockerty and Scheifly (1955) record an interesting case in which intermittent pressure on an isolated testicular metastatic nodule resulted in paroxysmal flushing.

Now that the carcinoid syndrome can be recognized during the patient's lifetime, assessment of the methods of treatment is of great importance. The speed of growth and spread of such tumours vary, but it has been shown that the primary can produce a detectable increase in urinary 5-H.I.A.A. before metastases have occurred (Sjoerdsma and others, 1956). This being so, an attempt at surgical resection represents the first step in the treatment of early cases. Indeed, since the disease apparently progresses slowly even after metastases have occurred, as demonstrated in this and many other cases, it may be of value to resect any large secondary deposits along with the primary growth to reduce the circulating blood-level of 5-H.T. As to medical measures, numerous experimental serotonin antimetabolites have been tried without significant clinical or biochemical improvement, e.g., ergotamine tartrate and dibenyline (Shaw and Woolley, 1953; Snow, Lennard-Jones, Curzon, and Stacey, 1955). Goble, Hay, and Sandler (1955) record temporary disappearance of flushing and bronchospasm following administration of colloidal radio-active gold. Lysergic acid di-ethylamide (L.S.D.), BOL 148 (a derivative of L.S.D.), and antihistamines have also been tried without success by Snow and others. Benditt and Rowley (1956) describe the experimental antagonism of 5-H.T. by chlorpromazine. This substance, given to our patient in a 14-day course of 25 mg. three times a day by mouth, produced no clinical change apart from drowsiness. Attempts to follow urinary excretion of 5-H.I.A.A. had to be abandoned since increasing diarrhœa made accurate 24-hour collections impossible.

SUMMARY

A case is described of malignant carcinoid with hepatic metastases, chronic endocarditis, pulmonary and tricuspid valvular stenosis, diarrhœa, and vasomotor disturbance observed over a 5-year period.

The cardiac lesions and the symptoms are apparently due to an excess of 5-H.T. (serotonin) produced by the tumour, and since the disease often progresses slowly, any reduction of the mass of tumour possible by surgical resection may be a valuable palliative treatment, even if the presence of metastases makes cure impossible.

Chlorpromazine, an experimental serotonin antagonist, given in therapeutic doses, did not alleviate the patient's symptoms.

Attention is drawn to a pronounced skin lesion, indistinguishable from pellagrous dermatitis, which was a feature of the clinical syndrome in our case and which responded to therapeutic administration of nicotinic acid.

Unsuccessful attempts were made, by venous occlusion plethysmography, to discover the nature of the peripheral vascular changes which occurred during skin flushing.

Acknowledgements.—We are grateful to many of our colleagues, with whom we discussed this case, for their advice. In particular, we wish to thank Professor J. H. Biggart, C.B.E., for advice on the autopsy findings; Professor D. C. Harrison for a urinary assay of 5-H.I.A.A.; Dr. R. F. Whelan and Dr. G. C. Patterson for the peripheral vascular studies; Dr. J. H. D. Millar for the electro-encephalogram report; Dr. J. A. Smyth and Mr. D. W. Neill, M.Sc., A.R.I.C., for biochemical assistance; and Mr. D. Mehaffy, A.R.P.S., Mr. R. G. Wood, and Mr. G. Smith for help with the illustrations.

REFERENCES

BARON, D. N., DENT, C. E., HARRIS, H., HART, E. W., and JEPSON, J. B. (1956), *Lancet*, **2**, 421.
BENDITT, E. P., and ROWLEY, D. A. (1956), *Science*, **123**, 24.
BIÖRCK, G., AXEN, O., and THORSON, A. (1952), *Amer. Heart J.*, **44**, 143.
DOCKERTY, M. B., and SCHEIFLY, C. H. (1955), *Amer. J. clin. Path.*, **25**, 770.
EVERED, D. F. (1956), *Biochem. J.*, **62**, 416.
FELDBERG, W., and SHERWOOD, S. L. (1954), *J. Physiol.*, **123**, 148.
FREYBURGER, W. A., GRAHAM, B. E., RAPPORT, M. M., SEAY, H. H., GOVIER, W. M., SWOAP, O. F., and VAN DER BROOK, M. J. (1952), *J. Pharmacol.*, **105**, 80.
GOBLE, A. J., HAY, D. R., HUDSON, R., and SANDLER, M. (1956), *Brit. Heart J.*, **18**, 544.
— — — — and SANDLER, M. (1955), *Lancet*, **2**, 1016.
HORSLEY, D. B., and PREC, O. (1956), *Arch. intern. Med.*, **97**, 806.
JENKINS, J. S., and BUTCHER, P. J. A. (1955), *Lancet*, **1**, 331.
JEPSON, J. B. (1955), *Ibid.*, **2**, 1009.
MCNEELY, R. G. D., and JONES, N. W. (1946), *Gastroenterology*, **6**, 443.
RODDIE, I. C., SHEPHERD, J. T., and WHELAN, R. F. (1955), *Brit. J. Pharmacol.*, **10**, 445.
SHAW, E., and WOOLLEY, D. W. (1953), *J. biol. Chem.*, **203**, 979.
SJOERDSMA, A., WEISSBACH, H., and UDENFRIEND, S. (1956), *Amer. J. Med.*, **20**, 520.
SMITH, J. P., and CAMPBELL, A. C. P. (1956), *J. Path. Bact.*, **72**, 673.
SNOW, P. J. D., LENNARD-JONES, J. E., CURZON, G., and STACEY, R. S. (1955), *Lancet*, **2**, 1004.
THORSON, A., BIÖRCK, G., BJÖRKMAN, G., and WALDENSTRÖM, J. (1954), *Amer. Heart J.*, **47**, 795.
TITUS, E. O., and UDENFRIEND, S. (1954), *Fed. Proc.*, **13**, 411.
UDENFRIEND, S., WEISSBACH, H., and CLARKE, S. T. (1955), *J. biol. Chem.*, **215**, 337.
WOOLLEY, D. W., and SHAW, E. (1954), *Brit. med. J.*, **2**, 122.

NEOPLASMS THAT GROW FROM THE BONE-FORMING ELEMENTS OF THE SKULL

A SURVEY OF 20 CASES

By G. F. ROWBOTHAM

FROM THE DEPARTMENT OF MEDICAL AND SURGICAL NEUROLOGY, THE ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE

THE compact osteoma of the vault of the skull is a familiar neoplasm, histologically being one of the most highly differentiated tumours in the whole realm of pathology. Its behaviour is essentially benign (*Fig.* 145).

Paranasal osteomata, on the other hand, as they enlarge are apt to compress the brain, cause meningitis, or dislodge the eyeball. Unlike their calvarial counterparts, they are often pedunculated, but are equally hard and as dense as ivory. Their histology varies a good deal from case to case and from one part of a growth to another.

The soft or spongy osteoma is a much rarer neoplasm. It invades the diploë of the vault or base, or both, and disturbs both inner and outer tables. Histologically it is relatively immature and differs in structure from case to case.

The osteochondroma, often clinically indistinguishable from the ivory osteoma, is readily differentiated by its histological structure. In this series of 20 cases, osteochondromata have been found not only in bones that develop from cartilage, but in bones of the vault that develop in membrane. The anomaly of a cartilaginous growth arising in a membranous bone will be discussed in some detail later.

A neoplasm composed entirely of cartilaginous tissue was encountered in this series in one instance only. It arose in the paranasal air-sinuses and was locally malignant.

Osteogenetic sarcomata, such as occur in the long bones of the limbs, must be exceedingly rare in the skull; indeed, it is doubtful whether they occur.

The primary object of this communication is to attempt to correlate the histology of these neoplasms that originate in the bone-forming organs of the skull and to give an account of their long-term behaviour, since some of the cases have been observed for as long as 20 years.

HISTORICAL SURVEY

It is not surprising that swellings on the skull have excited interest since early times. Galen was interested in this subject and recorded that the term 'exostosis' was given to swellings not only in the temples but in other parts of the body. That neoplasms of the skull appear early in the hierarchy of pathology is shown in the writings of Moodie (1926), Abbott and Courville (1939, 1945), and Krogman (1940). Moodie in his series of palæopathological studies described growths occurring in the heads of the pre-Columbian Indians of Peru. Abbott and Courville (1939), during an inspection of a collection of prehistoric skulls of the Pacific Slope, found neoplastic lesions in 20, 11 of which proved to be small osteomata of the cranial vault or external auditory canal. These two authors (1945) also quote Hooton's discovery of 'ivory excrescences' arising from the cranial bones during his inspection of a collection of skulls of the aborigines of North America. Krogman, when examining material excavated from an Iranian site at Tepe Hissar at the southern end of the Caspian Sea, found five skulls on which there were local mounds of bone. These skulls were thought to date back to 3000 B.C.

FIG. 145.—A compact osteoma of the vault of the skull in situ. (*From the Pathological Museum of the University of Manchester.*)

It was not until the middle of the nineteenth century that a serious attempt was made to sort into their true pathological groups the bony mounds that form on the skull. Rokitansky (1850) described the differences between hard and soft osteomata. It was Virchow (1865) who first attempted to differentiate the neoplastic from the non-neoplastic exostoses and gave us the first comprehensive classification of the osteomata. He thought that one type could change to another and back again during its life-history. Though numerous papers were written on the paranasal osteomata in the second half of the nineteenth century, little was said about the osteomata of the vault of the skull. Marey (1910) went so far as to say that the study of the osteomata of the vault had been a little neglected. It was Marey who gave the name 'le spongiostéome' to the soft variety of the neoplasm. A comprehensive survey of the literature on the subject up to that time is given in his paper. The subject of calvarial osteomata was later taken up by Echlin (1934), who described 7 cases from the collection of the Surgical Pathological Laboratory of the Johns Hopkins Hospital and details of 19 other cases collected from the literature were also given. It was Echlin who made the important suggestion that both the hard and soft varieties of

osteomata of the vault grow from the deeper layers of the periosteum, the soft variety invading the diploë by first eroding the outer table of the skull. Like Virchow, Echlin believed that hard osteomata could change to soft and back again.

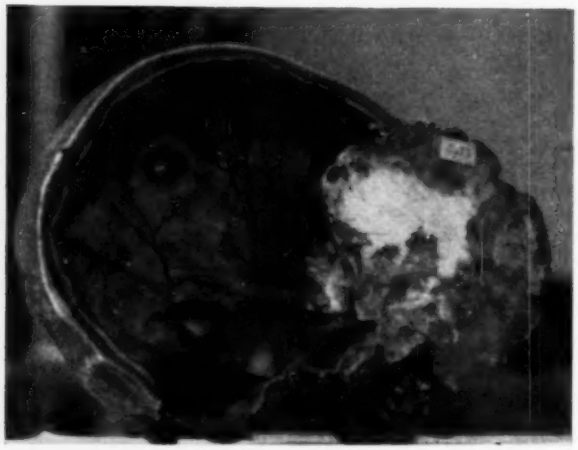


FIG. 146.—The tendency of the paranasal osteoma to encroach upon the intracranial and orbital cavities is well illustrated by this specimen. (*From the Cambridge Museum.*)

By the nature of their more dramatic appearance and their greater potential danger, it is not surprising that it was the paranasal osteomata that called most attention to themselves. Cruveilhier (1856) described them fully. Possibly it is to Dolbeau (1871) that the credit should be given for the most logical attempt to remove these tumours surgically, and he was the first to remove one successfully. Dolbeau stated that if the growth could be sufficiently widely uncovered, it could be lifted out 'comme un calcul de la vessie'. In a later paper, his pupil Richet (1871) made it clear that this was a somewhat optimistic view, since the tumour was pedunculated and attached by its neck to a wall of the sinuses and had to be fractured before it could be lifted free. In the nineteenth century the death-rate following the attempted removal of these tumours was high as a result of meningitis; indeed, one case of a successful removal was gleefully published by Knapp (1881). Paget (1865), in his *Lectures on Surgical Pathology*, described the ivory osteoma of the frontal bone and mentions a specimen in the museum at Cambridge (*Fig.* 146). Bland-Sutton (1903) stated that "an osteoma may be defined as an 'ossifying chondroma'". A comprehensive review of the subject was made by Armitage (1931), who described one case operated on by Cushing. Kessel (1953) discussed the diagnosis and treatment of 9 cases of osteoma of the paranasal sinuses with their complications. Rowbotham and Clarke (1955) described a new approach to the lateral sinus specifically designed for the removal of a paranasal osteoma. Andrew (1956) described 5 cases of osteoma of the paranasal air sinuses and advocated the turning down of a frontal bone flap for their removal. On the whole the contributions to this subject of osteomata of the skull by British authors have been sparse.

MATERIAL

The present series comprises 20 cases of different types of osteomata of the skull, details of which are given in *Table I.*

Ivory Osteomata of the Vault.—

General Statement.—There were 6 cases in this group; all were females, their ages ranging from 21 to 54 years. In no instance was there any significant history of injury, infection, or of any other irritating agent to account for the growths. They arose in the areas shown above.

Frontal	1
Parietotemporal	1
Parietal	2
Parieto-occipital	1
Temporomastoid	1
	6

Table I.—20 CASES OF OSTEOMATA OF THE SKULL

CASE No.	AGE	SEX	TYPE	SITE	LENGTH OF HISTORY TO FIRST EXAMINATION	TOTAL PERIOD OF OBSERVATION	RESULT
1	45	F.	Ivory	Parietotemporal	1 yr.	5 yr.	Cure
2	21	F.	Ivory	Parieto-occipital	7 mth.	2 yr.	Cure
3	51	F.	Ivory	Parietal	45 yr.	—	Cure
4	40	F.	Ivory	Parietal	5 yr.	—	Cure
5	25	F.	Ivory	Mastoid area	2 yr.	—	Cure
6	54	F.	Ivory	Frontal	16 yr.	—	Death
7	24	F.	Spongy	Frontal	8 yr.	—	Cure
8	40	F.	Spongy	Frontal	22 yr.	20 yr.	Cure
9	27	F.	Spongy	Occipital	26 yr.	10 yr.	Cure
10	32	M.	Spongy	Mid-frontal	10 yr.	—	Cure
11	39	M.		External-auditory meatus	1 yr.	—	Cure
12	30	F.	Paranasal	Frontal air-sinus	1 yr.	5 yr.	Cure
13	42	M.	Paranasal	Frontal air-sinus	1 yr.	5 yr.	Cure
14	39	M.	Paranasal	Frontal air-sinus	3 mth.	2 yr.	Cure
15	18	F.	Paranasal	Frontal air-sinus	7 mth.	2 yr.	Cure
16	58	F.	Paranasal	Ethmoidal air-sinus	6 mth.	—	Cure
17	27	M.	Osteochondroma	Parietal	8 yr.	2 yr.	Cure
18	32	M.	Osteochondroma	Temporal	8 yr.	4 yr.	Cure
19	62	F.	Osteochondroma	Frontal	5 yr.	9 yr.	Cure
20	19	M.	Chondroma	Frontal	2 yr.	1 yr.	Relief, but recurrence inevitable

All were uniformly hard to palpation; none were attached to overlying soft tissues and there were no abnormal changes in the overlying skin.

Appearance at Operation.—All the tumours were covered with a thick layer of fibrous tissue continuous

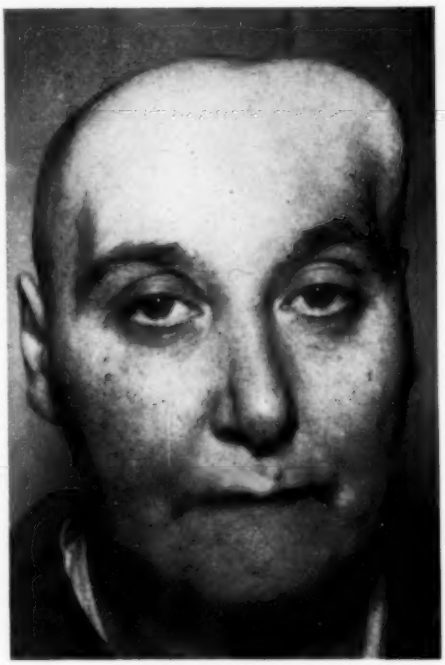


FIG. 147.—*Case* 6. A large compact osteoma of the skull.

with the surrounding periosteum. In 5 instances the growths formed sessile hemispherical mounds; one was pedunculated and L-shaped. The largest swelling measured 4½ in. in diameter and stood 2 in. above the normal level of the skull (*Fig.* 147), and the smallest measured 1 in. across and stood ½ in. high.

The swellings were obvious mounds of hard bone rising from the outer table of the skull. In the L-shaped case, the impression was that the growth had been turned back on itself by the resistance of the galea aponeurotica. In no instance was there increased vascularity in the tumour or in the surrounding bone.

The tumours were removed by block resection. In no case was there bulging of the inner table of the skull. Only in *Case* 6 was there any difficulty in separating the inner table from the dura mater. In every instance the impression was that of dealing with a solid piece of bone, there being no sign of any kind of malignancy.

A cross-section of the specimen in *Case* 3 shows clearly how the growth arose from the outer table of the skull to project outwards, leaving both tables and the diploë virtually intact (*Fig.* 148).

Radiographic Features.—

Clinical: All the growths showed as uniformly dense shadows without the slightest indication of normal bony architecture. They all arose from the outer table, one being L-shaped and the other four hemispherical.

On section of the specimens: In *Cases* 1, 2, and 3 no kind of patterned architecture was discernible. *Fig.* 149 shows the appearances in *Case* 6, which are unusual. Here the picture is that of lamellæ running radially outwards from the outer table. Though this appearance may, to some extent, have been due to stripping of the periosteum by the growth, there is

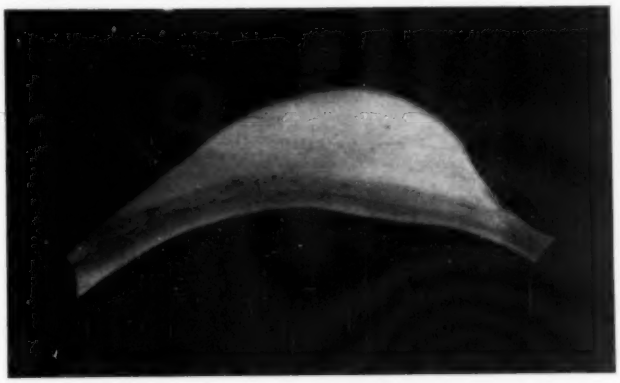


FIG. 148.—*Case* 3. A photograph of a slice taken through a compact osteoma of the vault of the skull.

FIG. 149.—Radiograph of a slice taken from the specimen in *Case* 6. Spiculation as shown here is rare in a compact osteoma.

no doubt that the mass of the swelling was neoplastic in nature and not reactive.

Histological Picture.—In every instance thin vertical sections were made through the whole thickness of the growth. The bone was slowly decalcified and stained by the following methods: H. and E., Mallory, and van Giesen.

At the outset it became clear that only by traversing the whole thickness of an osteoma can its true nature be detected. From small isolated sections it is often difficult to tell whether or not a specimen is merely a simple reactive exostosis.

Here it will be helpful if some of the salient features of bone structure are briefly reviewed.

Bone tissue consists of a collagenous matrix composed of fibrils embedded in a homogeneous protein substance (cement), the whole being rendered rigid by the deposition of calcium salts in a finally divided state. The fibrils of the bone matrix are collected into bundles forming coarse or fine fibres and the microscopical appearance of bone tissue depends largely on the size and arrangement of these fibres. Also the bone-cell spaces and their canals, in which lie the bone-cells and their processes, are dependent on the fibre arrangement.

Bone can be divided into two main histological types, lamellar and woven.

Lamellar bone can either be compact or cancellous; it is laid down in an orderly fashion according to an orderly pattern. In compact bone there are Haversian systems which consist essentially of a central canal containing blood-vessels, around which are laid horizontal lamellæ. Each Haversian system is separated from adjoining systems by means of the cement lines. Lamellar bone is characterized histologically by the fact that its fibres are fine and of uniform thickness and are arranged in sheets. In each sheet, which forms a single lamella, the general direction of the fibres is the same. Haversian systems may run at angles to each other, but when this happens there is an obvious pattern.

A B

FIG. 150.—*Case* 9. A spongi-osteoma arising in the occipital area, before and after operation.

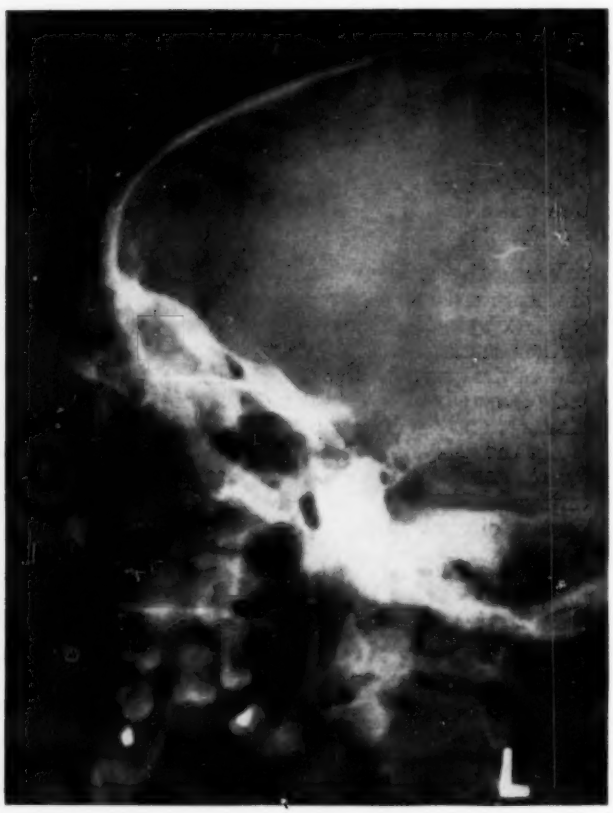
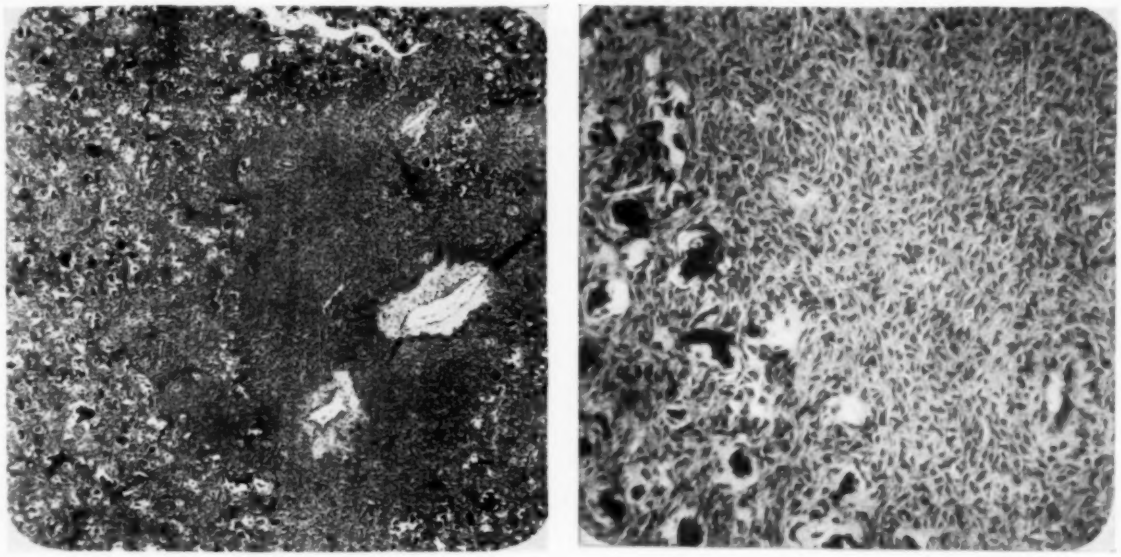


FIG. 151.—*Case* 8. Radiograph of a spongi-osteoma showing expansion of the tables of the floor of the frontal fossa with diploic extension of the tumour beyond the boundaries of the swelling.

Non-lamellar or woven bone forms the bony skeleton of the embryo. By the end of the first year of life nearly all the skeleton has been transformed to lamellar bone. Woven bone is commonly seen in pathological states of bone; however, even woven bone in a pathological state can be replaced by lamellar bone. Woven bone is characterized histologically by the fact that the fibrils of the matrix are collected into bundles, forming fibres of varying diameter which criss-cross one another in different directions, forming an irregular woven feltwork. Woven bone is often deposited in the form of irregular coarse trabeculæ. When these trabeculæ of woven bone are first formed, their margins are ill-defined and brush-like because the fibres of the matrix come out at right angles to the trabeculæ and enter the surrounding connective tissue. The bone-cells in woven bone are more numerous than in lamellar bone and more irregularly distributed. They are also larger and more irregular in shape. The canaliculæ are short and poorly developed, with few anastomoses. Unlike lamellar bone, woven bone may occasionally be formed by metaplasia of pre-existing connective tissue (Baker).

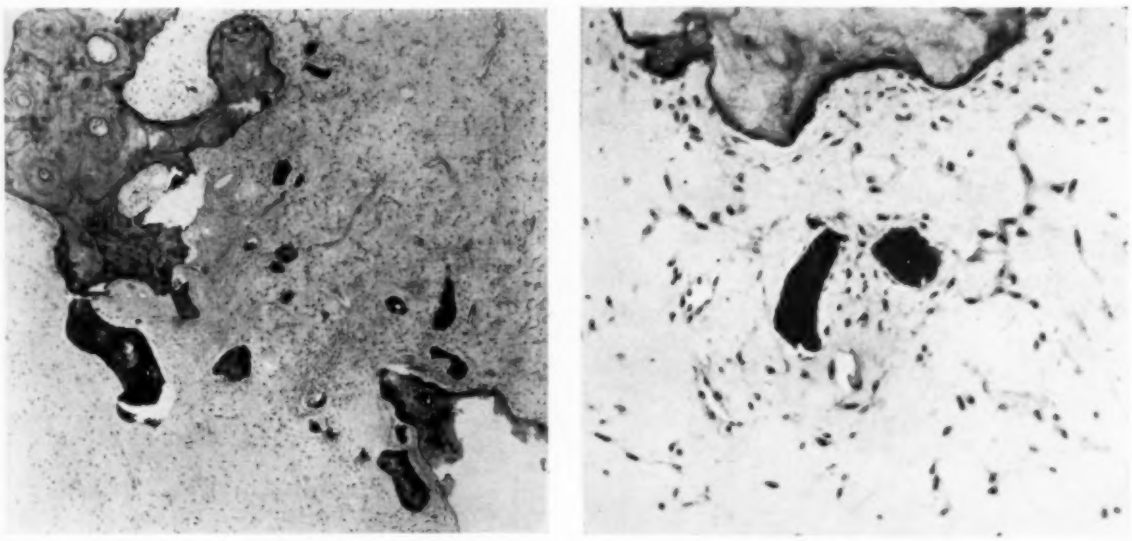
Histologically the general pattern in all six of the cases was much the same. In some areas there was an ordered architectural pattern almost indistinguishable from normal bone, whereas in others there was complete disorder in the pattern of the lamellæ, some branching off at random either at right angles or in spirals. In parts there were islands of bone having no connexion with the main mass of bone, being enclosed in matrix of differing maturity. Even in

the most compact zones of the osteoma there were inconsequential breaks in the bone structure, the gaps being filled with fibroplastic material in different degrees of development. Even in the most highly developed part of the tumours the clear-cut Haversian system of normal bone was imperfect. Here and of structure and order. In *Case* 6 the outer table had obviously been affected and to some extent the growth had entered the diploë. There is little doubt, however, from the overall picture that the growth arose from the outer table of the skull and that much of the mass was neoplastic and not periosteal reaction



A B

FIG. 152.—*Case* 7. The histological picture of a diploic fibroblastoma which is probably the immature stage of a spongy or soft osteoma. Hæmalum and eosin. (A, × 40; B, × 125.)



A B

FIG. 153.—*Case* 8. An example of the more immature form of spongi-osteoma, showing the early efforts of bone formation in membrane. Hæmalum and eosin. (A, × 40; B, × 125.)

there were bands of osteoid tissue which is that very early stage when bone first begins to take on its characteristic structure; in other words, osteoid tissue shows as the ghost of adult bone.

The picture of fibrous tissue was also variable. In some areas fibroblastic cell formation would be rich and the cells well formed, whereas in other places the matrix would consist merely of an amorphous mass. The overall picture, however, was that of bone that had not quite reached its full perfection to stripping. It is surprising how little reaction an osteoma arouses in the bone in which it forms. In *Case* 6 the new bone on the inner surface of the inner table is probably reactive and due to vascular influences.

As shown from the histories and as proved by the histological appearances, these tumours are essentially benign and show little or no tendency to encroach on the intracranial cavity. The only reasons for their removal are cosmetic ones, and

paring down, rather than block resection, is probably all that is needed to control their growth.

Spongio-osteomata of the Skull.—

General Statement.—There were 4 cases; 3 patients were female and one was male, their ages ranging from 24 to 40 years. The growths affected the occipital bone in one instance (*Fig.* 150) and the frontal part of the head in the other three instances.

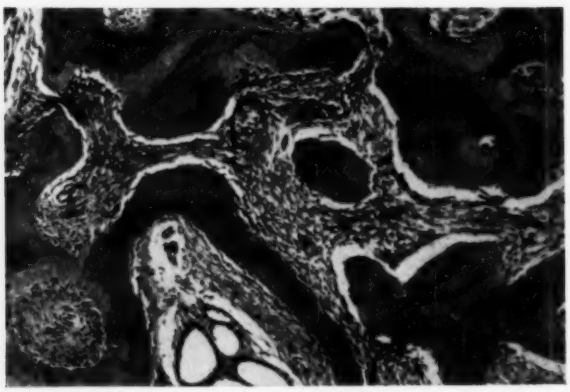


FIG. 154.—*Case* 10. A spongi-osteoma in which attempts at bone formation are well marked. (× 100.)

Up to the time of the first examination all the growths were known to have existed for at least 8 years. Clinically, though the swellings were more extensive they were much less circumscribed than in the ivory osteomata of the vault.

Radiographic Features.—The neoplasm showed as a diploic mass, both the inner and outer tables being expanded. Radiography also clearly showed that the neoplasms extended far beyond the boundaries of the clinical swelling (*Fig.* 151).

Appearance at Operation.—The operative picture was totally different from that of the ivory osteomata of the vault. Whereas in the ivory osteomata the swellings arose almost exclusively from the external table of the skull with few diploic changes, the spongio-osteomata were essentially diploic tumours. Both tables of the skull were expanded and were thinned. In every case the tumour material in the

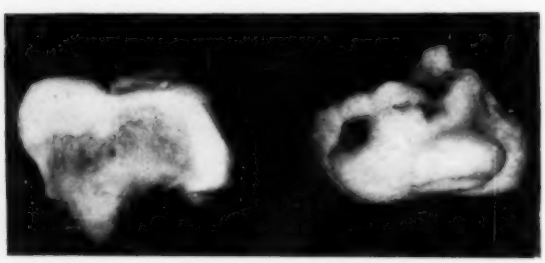


FIG. 156.—*Case* 12. A paranasal osteoma showing a central area of fibrocancellous bone and an outer casement of compact bone.

diploë was fibrous and gritty and its colour was dark grey with an occasional red tinge. The tumours were almost completely bloodless. In all cases the inner table was easily separable from the dura mater and in no case had the bony tables been perforated or the soft tissues invaded. Diploic invasion had extended well beyond the boundaries of the calvarial swelling.

Histological Picture.—*Case* 7 was the most primitive of the four growths. Nothing resembling bone or osteoid tissue was found. Here and there were nodes of calcification. The overall picture was that of an irregularly arranged fibrous matrix, in which were dotted islands of dense calcification. Indeed, the picture in many ways resembled a dural fibroblastoma or meningioma of the meningothelial

FIG. 155.—*Case* 16. An aerocele associated with an ethmoidal osteoma.

type. Scattered about were zones in which definite cellular structure could not be identified. The tables of the skull, though thinned, were not directly involved in the neoplastic process, their thinning and expansion being reactive to the pressures of the tumour. These points are shown in *Fig.* 152.

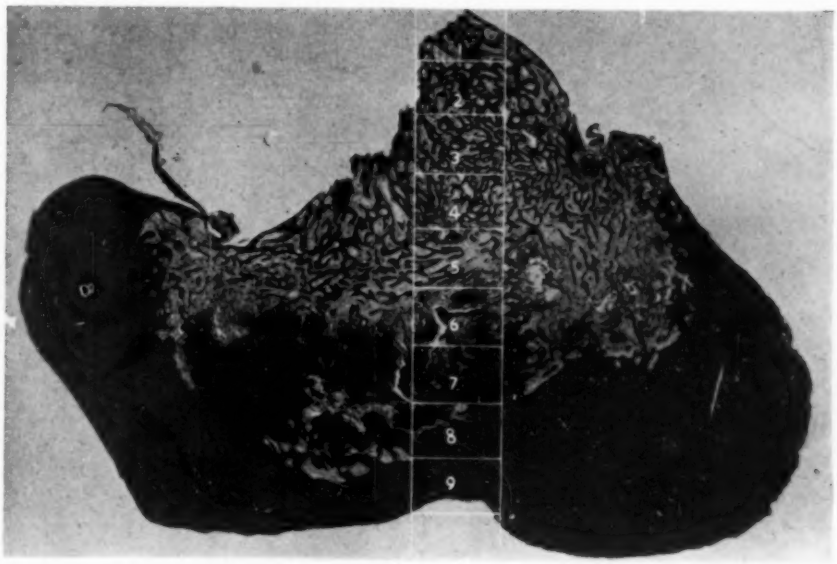
The tumour in *Case* 8 was much more mature than that in *Case* 7. Here and there were isolated areas in which bone formation was being seriously attempted. Scattered about were nodes of calcium. The matrix was less cellular than in *Case* 7, being composed of fibroblasts embedded in a mass of cement such as is seen in the early developmental stages of normal bone (*Fig.* 153). On the other hand, the picture was completely unlike that seen in the highly differentiated compact osteoma of the vault.

In *Case* 9 the tumour was more mature than that in *Case* 8. Here the fibrous tissue was well formed and well organized; it was enclosed in a lacework such as is seen when actual bone is about to develop. Bony trabeculæ were present here and there, but the fibrous tissue was much more abundant than the bone. The trabeculæ were isolated and in no part of the tumour was there a picture of an ordered bony architecture. Along some of the margins of the bony trabeculæ were multinucleated cells and undoubted osteoclasts (*Fig.* 154).

Histologically the growth in *Case* 10 resembled that in *Case* 9, the difference being that here the bone was in equal quantities with the fibrous tissue. Again there was no ordered architecture.

In *Case* 11 the tumour was composed largely of compact bone. No cartilage was present.

Osteomata of the Paranasal Air-sinuses.—*General Statement.*—There were 5 cases; 3 patients were female and 2 were male, their ages ranging from 18 to 58 years. In 4 cases the growths arose in the frontal air-sinus, and in 1 case the ethmoidal air-sinus was affected. Complications



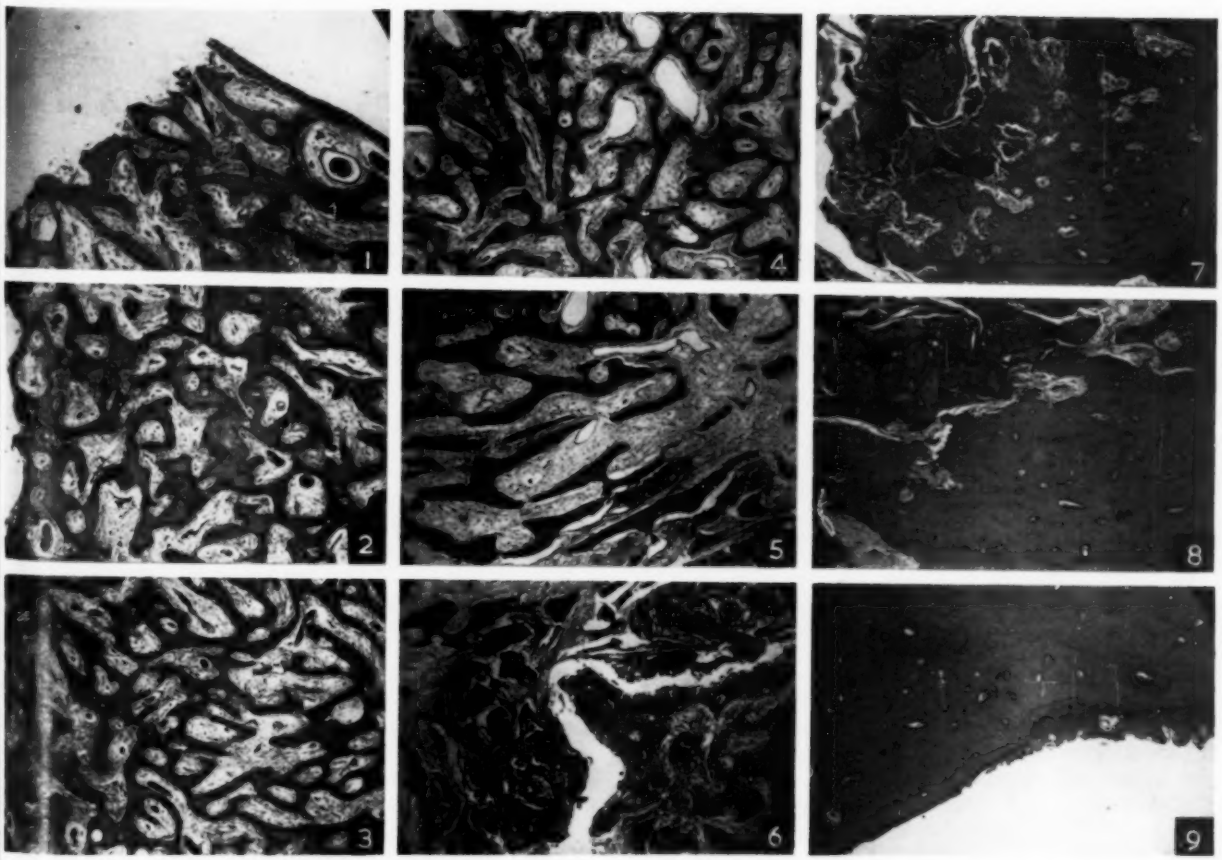


FIG. 157.—A histological traverse across a paranasal osteoma showing an outer case of compact bone and an inner core of cancellous tissue. Hæmatoxylin and eosin. (× 25.)

occurred in 3 instances; the ethmoidal growth was associated with an extensive aerocele of the brain (*Fig.* 155) and in the other two cases the eyeball had been displaced downwards, with cellulitis of the orbit in one instance. (Rowbotham and Clarke, 1955.)

Gross Appearance of Tumour.—In *Case* 12 the tumour was shaped like a molar tooth, its actual size and appearance being shown in the accompanying photograph (*Fig.* 156). Its surface was smooth, white in colour, and highly polished. At operation it was broken free from its attachment quite easily. On cross-section there was a core of fibrous tissue.

FIG. 158.—*Case* 13. A typical paranasal osteoma.

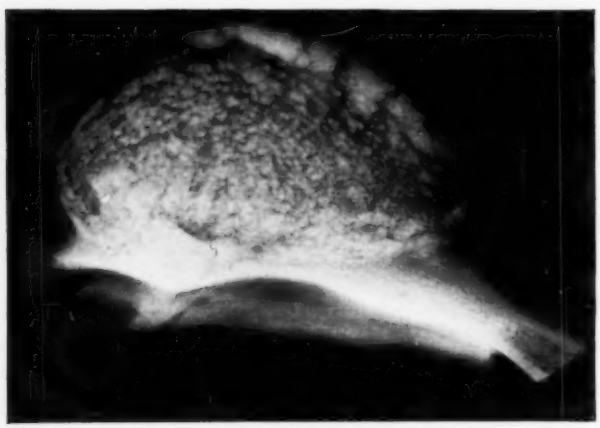


FIG. 160.—*Case* 17. Radiograph of a thin slice of an osteochondroma of the skull

The appearances were so strongly those of a tooth that special tests were made for dentine, but these proved to be negative.

Histologically this tumour consisted of an outer casing and an inner core. The outer casing was composed of dense compact bone without distinct lamellar architecture, but enclosing numerous small empty spaces which possibly were blood-channels, but which more likely contained fibrous tissue which had been removed during the histological processes. The core was composed of thick irregularly arranged trabeculæ of woven bone. These trabeculæ were embedded in a matrix of fibrous tissue, the cells of which were spindle-shaped, sparse, and whose processes formed a network. Within this network were large blood-vessels with well-formed walls. No trace of cartilage could be found. There were areas where the fibrous matrix was in the very early stages of calcification. Scattered along the margins of the trabeculæ were occasional multinucleated cells (*Fig.* 157).

The tumour in *Case* 13 measured 2 in. in length and 1 in. in width and thickness. Its surface was nodular and it was greyish-white in colour; it was not particularly highly polished (*Fig.* 158). Cross-section proved that it was composed of solid bone with no core or fibrous tissue. At operation this tumour also broke easily away from its attachment.

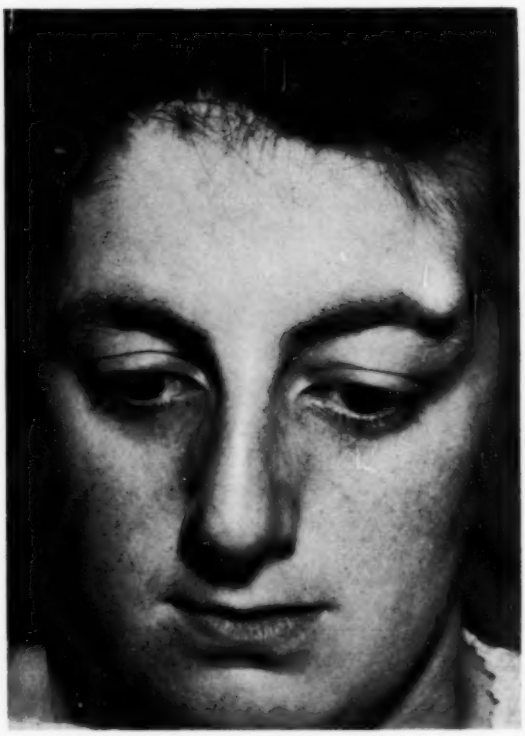


FIG. 159.—*Case* 15. The swelling of a paranasal osteoma which has encroached upon the orbit.

Histologically this was a typical compact osteoma of imperfect adult bone architecture. There were isolated areas of fibroblastic tissue.

In *Case* 14 the tumour was nodular and bony-hard, but was easily picked from the frontal sinus at operation. The orbital roof had been eroded and broken into and there was orbital cellulitis. The eyeball had been displaced. This case has been published in detail elsewhere. (Rowbotham and Clarke, 1955.)

Histological examination showed the appearances of a compact osteoma. Again the typical lamellar pattern was absent and there were irregular islands of fibrous tissue. Here and there was evidence of osteoblast and osteoclast activity.

In *Case* 15 the tumour projected into the orbit and there was slight downward displacement of the eyeball (*Fig.* 159).

Histologically the tumour was much less compact than is usual in paranasal osteomata, there being

almost as equal an amount of fibrous tissue as of bony tissue. Again the bony tissue lacked the ordered architecture of normal bone.

The growth in *Case* 16 consisted of a pointed mound of bone arising from the ethmoid plate, being

FIG. 161.—*Case* 17. Microphotograph of a traverse through the whole breadth of an osteochondroma of the skull. Hæmatoxylin and eosin. (× 25.)

about ½ in. in diameter and ½ in. high. Its apex was firmly attached to the dura mater.

Histologically the specimen consisted of an outer casing of hard bone and an inner core of fibrous tissue.

Osteochrondromata of the Vault of the Skull.—There were 3 cases, two males aged 27 and 32 years, and one female, aged 62 years.

In *Case* 17 the patient, a man of 27 years of age, was first seen in 1950. In 1942 he had noticed a hard swelling about the size of a pea behind the left ear. The swelling increased in size until in 1950 it measured 6 cm. in diameter and stood 4 cm.

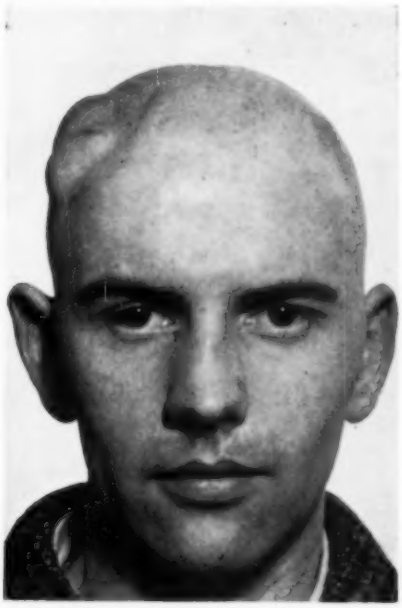


FIG. 162.—*Case* 18. A recurrent osteochondroma of the skull.

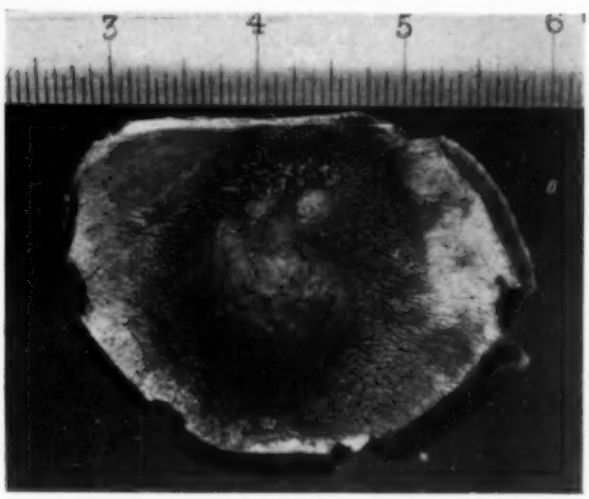


FIG. 163.—*Case* 18. Gross specimen of recurrent osteochondroma of the vault of the skull, showing a degree of intracranial protrusion.

above the surrounding bone. Clinically there was no evidence of intracranial extension. Radiology showed a dense and speckled swelling on the top of the left mastoid process.

At operation the outer surface of the swelling was found to be smooth and glistening and not attached to the soft tissues. The inner surface was also smooth and not attached to the dura mater. There was no encroachment on the intracranial cavity. The whole swelling was as hard as bone. Removal was effected by block resection. Radiographs of a thin slice of the tumour showed a densely

speckled swelling (*Fig.* 160). The histology of this neoplasm is shown in some detail in *Fig.* 161.

In *Case* 18 the patient, a man aged 37 years, first attended hospital in 1937 complaining of a lump on the right side of his head in the fronto-parieto-temporal junction. At that time it was a hemispheral swelling standing about ½ in. high and measuring 1 in. across. By turning down a horseshoe-shaped flap the tumour was exposed and cut off level with the rest of the skull (A. R. D. Pattison); to naked-eye appearance it was judged to be a chrondroma. Recurrence was rapid and removal on the second occasion was effected by block resection (A. R. D. P.). The tumour this time was proved by histology to be a chondroma.

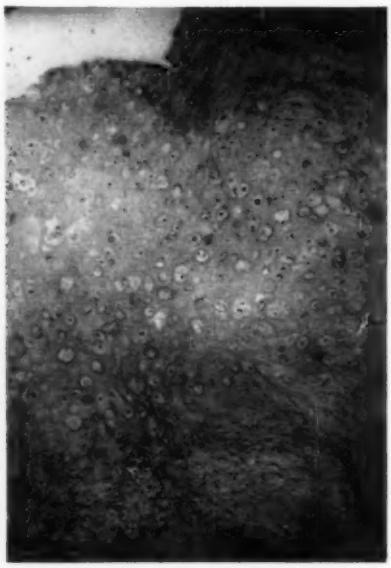


FIG. 164.—*Case* 19. Microphotograph of an osteochondroma. This neoplasm occurred on the vault of the skull in a bone that develops in membrane. Hæmatoxylin and eosin. (× 85.)

I first saw the patient in 1941. The clinical photograph shows the features of another recurrence (*Fig.* 162). The tumour was again removed by block resection (G. F. R.) and the accompanying photograph shows the size of the swelling (*Fig.* 163). In consistency the tumour was leathery; it stripped quite easily from the dura mater and there was no suggestion of invasion of the brain or the dura mater. Histologically it proved to be an osteochondroma.

In *Case* 19 the history was that of a slowly growing swelling on the frontal bone in a woman 62 years of age. Clinically it was thought to be a simple osteoma with no special clinical features and with no signs or symptoms to point to an intracranial extension. The only abnormal radiographic feature was the lack of calcification at the summit of the tumour which was otherwise densely calcified. Removal was effected by block resection in 1942, since when there has been no recurrence. Histologically the neoplasm was proved to contain cartilage.

Comment.—Since in *Case* 17 the swelling occurred at the base of the skull, the presence of cartilage is not surprising because the mastoid process of the temporal bone, which was partly covered by the tumour, develops in cartilage. On the other hand, the presence of cartilage in a neoplasm arising primarily in bone that develops exclusively in membrane calls for particular consideration. In the first instance it must be established beyond all reasonable doubt that the tumour did, in fact, contain cartilage and that we were not seeing some phase of membranous bone development that might closely mimic the appearance of cartilage.

FIG. 165.—*Case* 20. Erosion of the skull by a chondroma.

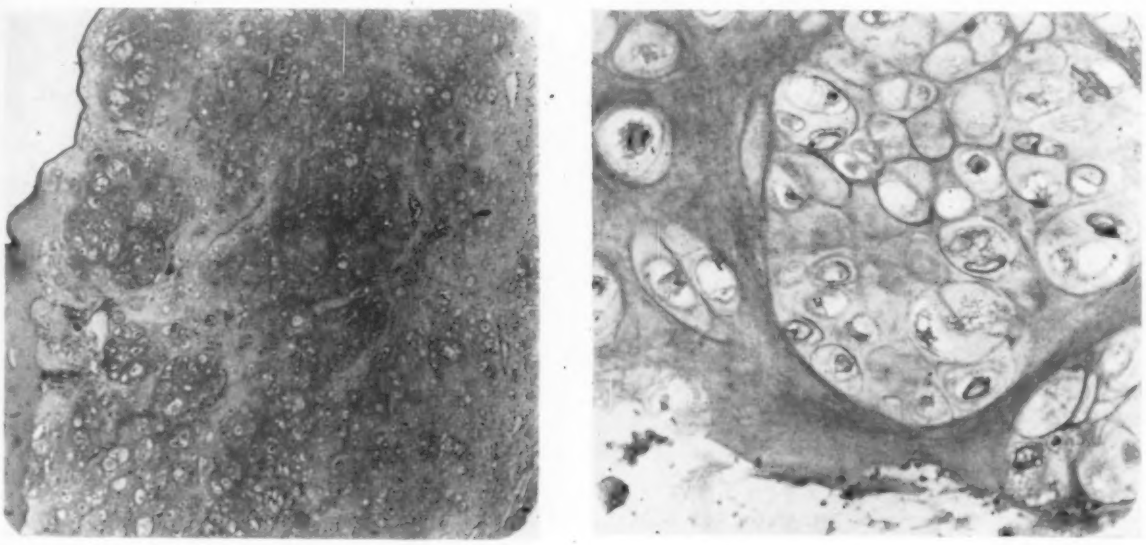
In *Case* 18 there is no doubt that the naked-eye appearances of the second recurrence were typical of a piece of cartilage. Also, Professor A. F. Bernard Shaw, the late Professor of Pathology in the University of Durham, described areas of cartilage in the histological section.

In *Case* 19 the accompanying histological picture (*Fig.* 164) speaks for itself.

In these two particular cases the most likely explanation seems to be that islands of cartilage become segregated as a result of some minor developmental anomaly. It is also strange that in this series cartilage was never found in the paranasal osteoma as these neoplasms arise in an area of the skull where some of the bone develops in cartilage.

Chondromata of the Skull.—There was one case, the patient being a man aged 19 years. The history was of a small swelling on the left side of the forehead first noticed in 1932; it increased slowly in size and later in the same year a biopsy was taken, histology proving the growth to be a pure chondroma. The man first attended the neurosurgical clinic in Manchester in November, 1934, complaining of double vision and of neuralgic pains in the left side of the head.

At that time the swelling measured ½ in. in diameter and was hemispherical in shape; it was attached to bone but not to the skin and was rubbery in consistency. Bulging into the upper part of the orbit was another swelling of the same consistency, the left eyeball being displaced downwards and outwards. Radiography showed an erosion of both frontal bones with crenated clear-cut margins, the extent of which is illustrated in *Fig.* 165. The outline of the left orbit was distorted and a fuzzy swelling projected into the cavity from above. The left frontal sinus had disappeared in the pathological changes. The picture was suggestive either of mucocele or of benign neoplasm of the skull.



A B

FIG. 166.—Microphotograph of a chondroma of the skull. Hæmalum and eosin. (A, × 40; B, × 150.)

At operation, a curved incision was made in the line of the left eyebrow and the soft tissue retracted subperiosteally. Towards the inner end of the wound a glistening encapsulated mass of neoplastic tissue had broken through the outer table of the skull. By nibbling away the outer table of the skull more of the neoplasm was exposed and was found to extend along the orbital walls as far as the sphenoidal fissure. A large nubbin of tumour projected into the orbit, displacing the eyeball. On making a small hole through the inner table of the skull a massive extension of the neoplasm could be detected in the frontal fossa. A large quantity of the swelling was removed piecemeal, particular effort being made to provide adequate decompression of the orbit; because of its extent the tumour could not be completely removed. The operation was more or less bloodless. As far as could be judged, the origin of the tumour was in the bones of the base of the skull, the frontal bone being invaded by extension along the diploë.

Recovery was uneventful. The eyeball returned to its normal position and the man was relieved of his diplopia. Histologically the tumour was proved to be a pure chondroma (*Fig.* 166).

Within a few months the patient was readmitted to hospital with obvious symptoms and signs of cerebral compression due to recurrence. On further operation, on turning down a frontal bone flap, both frontal fossæ were found to be filled with tumour. Both frontal lobes had been pushed upwards and backwards; the dura mater was intact, the tumour lying entirely extradurally. By means of a sharp spoon large amounts of the tumour were removed. The histological picture was that of a chondroma.

Track of this patient was soon lost and probably he succumbed early from a further recurrence.

CONCLUSIONS

In the skull, as elsewhere in the body, neoplasms that are composed entirely or largely of cartilage are apt to be malignant and certainly recur if not cleanly removed. On the other hand, osteomata, whether of the soft or hard variety, are essentially benign. Though the soft variety is apt to undergo rapid bursts of growth and give the impression of malignancy, these bursts are usually self-limiting and cease before serious damage is done. Indeed, soft osteomata may grow for twenty years before encroaching on the intracranial cavity.

It is singular how rarely, if ever, cartilage is found in the paranasal osteomata. This type of neoplasm is often seen in routine examination of the skull, but such tumours need not necessarily be removed in every case. The only absolute indications for removal are enlargement beyond the confines of the sinus itself and sinus infection.

The histology of the hard osteomata can prove a very difficult diagnostic problem, particularly if only small and isolated fields of a specimen are examined. The only safe way to determine the nature of a bony swelling is to take a wide traverse across its whole thickness, as has been done in this series.

The conception of a single cell turning malignant to grow into a space-occupying neoplasm that invades the remaining bone and nearby tissue is an attractive one because it is simple. In the case of bony neoplasms, my histological studies suggest that a whole section of bone loses its normal controls of growth

and function and that the neoplasm results not from a single disordered cell, but from the activity of this disordered system. As a neoplasm grows it tends to strip the periosteum to cause reactive bone formation.

Many bony tumours, I believe, are a combination of neoplastic and reactive bone. Right-angle spiculation, so commonly seen in body tumours, is much more likely to be reactive than neoplastic. There is, in bony tumours as in neoplasms elsewhere in the body, a wide variance in the histological picture: not only from one growth to another but from one part of a growth to another part. The impression that I gained from this series is that every phase in the development of bone is paralleled by its neoplastic counterpart.

SUMMARY

Twenty cases of different types of osteomata of the skull are described and the histological pictures portrayed in some cases. The life-history of a tumour has been known for 10–20 years, and an attempt is made to give some account of histopathological correlation to the various types of neoplasms that arise primarily in the bone-forming organs of the skull.

I would like to thank Mr. R. Ridley of the Department of Photography, King's College, Newcastle upon Tyne, for the quality of the illustrations, and Miss M. Bousfield and Miss A. Cairns for their help with the preparation of this paper. I am also grateful for a grant from the Research Fund of the Royal Victoria Infirmary.

REFERENCES

ABBOTT, K. H., and COURVILLE, C. B. (1939), *Bull. Los Angeles neurol. Soc.*, **4**, 101.
— — — — (1945), *Ibid.*, **10**, 19.
ANDREW, J. (1956), *Brit. J. Surg.*, **43**, 489.
ARMITAGE, G. (1931), *Ibid.*, **18**, 565.
BAKER, S. L. (1950), *A Text-book of X-ray Diagnosis*, ed. S. C. Shanks and P. Kerley, **4**, 55. London: Lewis.
BLAND-SUTTON, J. (1903), *Tumours, Innocent and Malignant: their Clinical Characteristics and Appropriate Treatment*. 3rd ed. Chicago: W. T. Keener & Co.
CRUVEILHIER, J. (1856), *Traité Anat. pathol. gen.*, **3**, 869. Paris: Baillière.
DOLBEAU, H. F. (1871), *Mém. Acad. Méd. Paris*, **30**, 1; original contribution, *Bull. Acad. Méd. Paris*, **31**, 1076.
ECHLIN, F. (1934), *Arch. Surg.*, **28**, 357.
GALEN (1824), *Opera*, ed. C. G. Kuhn, **7**, 728. Leipzig: Cnobloch.
KESSEL, F. K. (1953), *Helv. chir. acta*, **20**, 83.
KNAPP, H. (1881), *Trans. med. Soc. St. N.Y.*, **21**, 252.
KROGMAN, W. M. (1940), *Bull. Hist. Med.*, **8**, 28.
MAREY, G. (1910), "Contribution à l'étude d'une variété particulière d'exotose de la voûte cranienne, le spongiostéome". *Thèse de Paris*, No. 87.
MOODIE, R. L. (1926), *Ann. med. Hist.*, **8**, 394.
PAGET, J. (1865), *Lectures on Surgical Pathology*, 3rd Amer. ed., 477.
RICHET, D. D. A. (1871), *Bull. Acad. Méd. Paris*, **36**, 564.
ROKITANSKY, C. (1850), *A Manual of Pathological Anatomy*, **3**, 122. London: The Sydenham Society.
ROWBOTHAM, G. F., and CLARKE, P. R. R. (1955), *Brit. J. Surg.*, **42**, 1.
VIRCHOW, R. (1865), *Die Krankhaften Geschwülste*, **2**, 30. Berlin: A. Hirschwald.

INTERNAL CAROTID THROMBOSIS AND SPONTANEOUS PNEUMOCEPHALUS AFTER HEAD INJURY*

By R. ALEX DAWS

FROM THE DEPARTMENT OF NEUROSURGERY AT THE CARDIFF ROYAL INFIRMARY

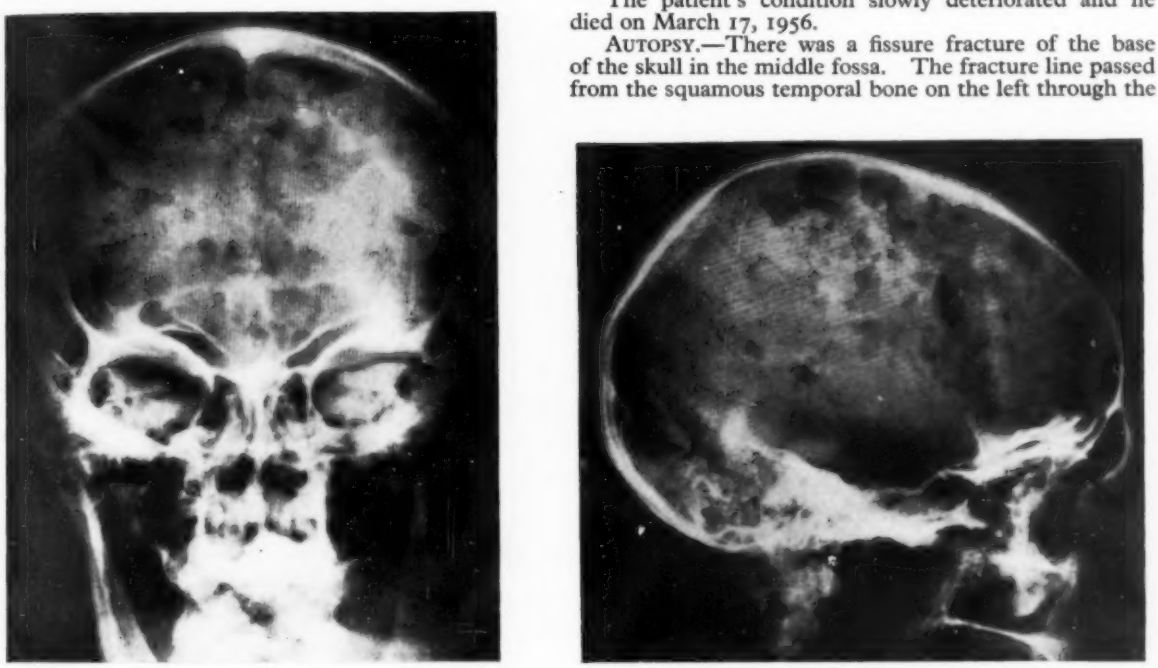
THROMBOSIS of the internal carotid artery was at one time considered to be a rare occurrence. Cerebral angiography, however, has corrected this false impression and the condition is now frequently demonstrated during life. The various clinical manifestations which may follow occlusion of this vessel and the angiographic appearances are well established.

Internal carotid thrombosis may be due to several causes. Elvidge and Werner (1951), from a study of the literature, stated that arteriosclerosis and thrombo-angiitis obliterans were the two most frequent aetiological factors. Thrombosis of the carotid vessels has been described as a result of direct trauma of the wall of the artery by penetrating wounds of the neck (Whalley, 1946; Caldwell and Haddon, 1948). Braudo (1956) has reported internal carotid thrombosis in children after injury in the region of the soft palate. Thrombosis may also follow non-penetrating injury to the neck (Northcroft and Morgan, 1944; Schneider and Lemmen, 1952; and Clarke, Dickson, and Smith, 1955). Boldrey, Maass, and Miller (1956) have discussed compression of the internal carotid artery by the lateral process of the atlas as an aetiological factor in some cases of the disease. Little attention appears to have been paid to the fact that head injury may play a direct part in precipitating thrombosis in this artery. The late Sir Hugh Cairns (1942) reported a case which followed a head injury, and quoted another case from the literature. Sedzimir (1955) has reported a further 7 cases in which the thrombosis resulted from trauma to the skull.

The importance of injury to the head in a case of internal carotid thrombosis is almost impossible to assess when the trauma occurs long before clinical evidence of such a lesion becomes apparent. When, however, thrombosis of the artery with disturbance of neurological function follows immediately, or within a few hours of a head injury, the relationship can be accepted. The following report describes a case of head injury which was complicated three hours after the accident by internal carotid thrombosis

* From the Department of Neurological Surgery, Morriston Hospital, Swansea.

and, in addition, by spontaneous pneumocephalus. As in the case reported by Cairns (1942), and in three of the cases reported by Sedzimir (1955), a fracture of the base of the skull close to the internal carotid artery was revealed at autopsy. In the case reported here thrombosis had occurred just below the base of the skull and had involved the intracranial segments of the artery. Distally the thrombus entered the right anterior and middle cerebral arteries.



A B

FIG. 167.—A, Anteroposterior, and B, lateral, radiographs of the skull showing extensive pneumocephalus.

CASE REPORT

The patient, a 55-year-old man, was admitted as an emergency on March 13, 1956. He had been struck on the left side of the face by a plank of wood and was thrown backwards striking his head on a wall. Consciousness was lost for only a few seconds.

ON EXAMINATION.—On admission to hospital he was conscious but a little confused. There was an extensive abrasion over the left side of his face and bruising of the scalp in the right occipital and mastoid regions. The mandible was fractured near to the symphysis. As a result of this, and the associated swelling of the tissues in the floor of the mouth, there was some respiratory obstruction with slight cyanosis. No abnormal physical signs were demonstrated in the central nervous system at that time. A clear airway was established and the patient transferred to the ward for observation.

Three hours after admission his condition deteriorated. There was slight clouding of consciousness and he developed a left hemiplegia with impairment of sensation on this side. X-ray examination of the skull revealed extensive spontaneous pneumocephalus (*Fig.* 167) but no fracture was demonstrated. There was no clinical evidence of injury to the neck and normal carotid artery pulsation was judged to be present on both sides. There was little further change in the patient's condition until the evening of March 15 when he developed signs of raised intracranial pressure. The right pupil became dilated, the plantar responses extensor, and he rapidly passed into coma.

AT OPERATION.—The usual exploratory burr-holes were made, but there was no evidence of an intracranial collection of blood. Air was found in the subdural space on both sides. The brain was under increased tension and the intraventricular pressure was high. The right hemisphere, in the frontal and temporal regions, felt soft to the exploring cannula, and necrotic brain oozed through the ruptured pia on withdrawing the cannula.

The patient's condition slowly deteriorated and he died on March 17, 1956.

AUTOPSY.—There was a fissure fracture of the base of the skull in the middle fossa. The fracture line passed from the squamous temporal bone on the left through the foramen spinosum, foramen lacerum, across the sella turcica, and into the right optic canal. The line then passed backwards through the right foramen lacerum, foramen ovale, and along the anterior surface of the petrous temporal bone. There was a small loose fragment of bone in the anterior wall of the sella to the right of the midline. In spite of a careful search the site of the dural tear could not be located. The sphenoid sinus was full of blood-clot.

There was extensive infarction of the right cerebral hemisphere. The right internal carotid artery was occluded by a thrombus commencing just below the base of the skull. The intracranial portion was thrombosed and the thrombus had extended into the right anterior and middle cerebral arteries. On histological examination atheroma was present in the internal carotid, most marked in the region of the siphon. In that part of the artery, just proximal to the siphon, a longitudinal tear in the media and intima was demonstrated. Thrombosis had occurred in this region and had extended both proximally, occluding the last 2 cm. of the cervical portion, and also distally into the intracranial portion, the middle and anterior cerebral arteries.

DISCUSSION

This case presented an interesting problem in differential diagnosis. Hemiplegia following a lucid interval after a head injury, and in the absence of obvious injury to the neck, is normally regarded as due to intracranial hæmorrhage. Such a possibility was considered, but seemed unlikely as the hemiplegia was known to have been of sudden onset, and was initially complete. Moreover, there was no

significant disturbance of consciousness. On these grounds thrombosis of a major artery, probably the right internal carotid, was diagnosed. No difference in carotid pulsation could be detected on the two sides of the neck. Internal carotid pulsation, however, is difficult to assess and Gurdjian and Webster (1953) did not think that differences in the degree of pulsation on the two sides could be depended upon for an accurate diagnosis.

Deterioration in the patient's condition forty-eight hours after the onset of the hemiplegia, with signs of raised intracranial pressure and deepening coma, cast doubt on the diagnosis and the usual exploratory burr-holes were made to exclude an intracranial collection of blood. Autopsy revealed the presence of internal carotid thrombosis and showed that the subsequent rise in intracranial pressure was due to infarction of the cerebrum.

When cerebral infarction and associated swelling of the hemisphere occurs as an early feature in cases of internal carotid thrombosis, particularly when there is a history of head injury, it is impossible to exclude an intracranial hæmorrhage on clinical grounds alone, and surgical exploration is necessary. A gross degree of cerebral swelling, however, is not often encountered in occlusion of the internal carotid artery. The early direct extension of the thrombotic process to involve the vessels of the circle of Willis was undoubtedly responsible for the extensive ischæmic change with gross disturbance of neurological function which occurred in this case.

Intimal tears of the internal carotid artery have been reported by Verneuil and Greco (quoted by Schneider and Lemmen, 1952), by Caldwell and Haddon (1948) and Northcroft and Morgan (1944). In all these cases damage to the wall of the artery followed injury to the neck. In the case reported here there was no evidence, either clinically or at autopsy, of trauma to the neck. The exact mechanics of the head injury could not be ascertained in this patient, though it is probable that the tear in the artery wall resulted from strains transmitted directly to the vessel by the head injury (Sedzimir, 1955).

Traumatic pneumocephalus, although now recognized with increasing frequency, remains a relatively rare occurrence. While there are other more unusual causes of the condition it is most commonly found in cases of closed head injury with fractures involving the paranasal air sinuses. In a survey of 308 such cases by Lewin (1954) intracranial air was demonstrated in 24 of the patients. The occurrence of pneumocephalus depends upon a fracture of the wall of an air sinus and a tear of the overlying dura mater and arachnoid, thus producing a communication between the meninges and the exterior. Increased intranasal air tension must also be present to force the air through the fistulous communication into the intracranial cavity where it may become trapped in the subdural space, subarachnoid space, ventricles, or occasionally in the substance of the brain. In this patient the partial respiratory obstruction which was present on admission must have been largely responsible for the very early occurrence of the pneumocephalus. In spite of a careful search at autopsy the site of the dural tear could not be identified. There was a loose fragment of bone in the fracture line in the anterior wall of the sella turcica. As the sphenoid sinus was the only air sinus involved by the fracture the fistula must have been in this region. Cerebrospinal rhinorrhœa was not present in spite of the gross degree of pneumocephalus. This was surprising as profuse rhinorrhœa is usually characteristic of sphenoidal sinus dural tears owing to their anatomical relationship to the cisterna chiasmatica, as has been pointed out by Lewin and Cairns (1951). The absence of rhinorrhœa can possibly be explained by the fact that at autopsy the sphenoid sinus was found to be completely obstructed by solid blood-clot, the organization of which might have resulted in a delayed onset had the patient survived.

SUMMARY

A case of internal carotid artery thrombosis and hemiplegia after a head injury is described. Spontaneous pneumocephalus also occurred as a complication. Aetiology and the problem of differential diagnosis are briefly discussed.

I wish to express my thanks to Mr. Norman Whalley for help in the preparation of this paper, and also for permission to publish the case admitted under his care. I would also like to thank Professor Lambert Rogers for his help and encouragement.

REFERENCES

BOLDREY, E., MAASS, L., and MILLER, E. (1956), *J. Neurosurg.*, **13**, 127.
BRAUDO, M. (1956), *Brit. med. J.*, **1**, 665.
CAIRNS, H. (1942), *Lisboa méd.*, **19**, 375.
CALDWELL, H. W., and HADDON, F. C. (1948), *Am. intern. Med.*, **28**, 1132.
CLARKE, P. R. R., DICKSON, J., and SMITH, B. J. (1955), *Brit. J. Surg.*, **43**, 215.
ELVIDGE, A. R., and WERNER, A. (1951), *Arch. Neurol. Psychiat., Chicago*, **66**, 752.
GURDJIAN, E. S., and WEBSTER, J. E. (1953), *J. Amer. med. Ass.*, **151**, 541.
LEWIN, W. (1954), *Brit. J. Surg.*, **42**, 1.
— — and CAIRNS, H. (1951), *Brit. med. J.*, **1**, 1.
NORTHCROFT, G. B., and MORGAN, A. D. (1944), *Brit. J. Surg.*, **32**, 105.
SCHNEIDER, R. C., and LEMMEN, L. J. (1952), *J. Neurosurg.*, **9**, 495.
SEDZIMIR, C. B. (1955), *J. Neurol. Psychiat.*, **18**, 293.
WHALLEY, N. (1946), *Brit. J. Surg.*, **33**, 400.

CUSHING'S SYNDROME

A REPORT OF THIRTEEN CASES AND THEIR SURGICAL TREATMENT

By D. A. D. MONTGOMERY

PHYSICIAN TO OUT-PATIENTS, ROYAL VICTORIA HOSPITAL, BELFAST

AND R. B. WELBOURN

READER IN SURGERY, QUEEN'S UNIVERSITY OF BELFAST

TWENTY-FIVE years ago Harvey Cushing (1932) described the syndrome which now bears his name. Since then enormous strides have been made in our knowledge of adrenal physiology, and it is now believed that the condition results from excessive secretion of adrenocortical hormones, particularly glucocorticoids, due either to an abnormality of the adrenal glands themselves, or to over-production of corticotrophin by the anterior pituitary. Except in cases of adrenal tumour it is rarely possible to determine the site of the primary lesion and we are using the term 'Cushing's syndrome' to include all patients who exhibit the clinical features described by Cushing. It is often easy to recognize the condition clinically, but biochemical tests are now available to assist in the diagnosis of doubtful cases. These tests involve the estimation of adrenal steroids in the urine both in the basal state and following stimulation with corticotrophin. The characteristic finding is an increased excretion of glucocorticoids (different fractions of which may be measured as 'reducing steroids', 17-hydroxycorticoids,* or 17-ketogenic steroids), and sometimes of androgens (which are measured as 17-ketosteroids). The pattern of excretion may also help to determine the nature of the responsible pathological lesion. Radiography may help to demonstrate tumours or hyperplasia in the adrenal glands.

The treatment of Cushing's syndrome is directed, logically, towards reducing the secretion of adrenocortical hormones, but there is no general agreement about the best method of achieving this result. No satisfactory form of drug treatment has yet been evolved. Testosterone was proposed by Albright, Parson, and Bloomberg (1941) with the object of inhibiting the corticotrophic activity of the anterior pituitary and of promoting protein anabolism, but, while it has been effective on occasions, it has usually failed to influence the disease (Cope and Raker, 1955). Potassium salts are of value only for restoring potassium deficiency. Recently, amphenone (1, 2-bis p-aminophenyl 2-methyl propanone-1 dihydrochloride), a drug which appears to inhibit directly the formation of corticosteroids, has been used in a few patients, but it is too toxic for general clinical use (Thorn, Renold, Goldfien, Nelson, Reddy, and Hertz, 1956; Hertz, Pittman, and Graff, 1956). It may well be the forerunner, however, of less toxic and more effective compounds. In the absence, therefore, of suitable drug therapy other methods have had to be employed. Pituitary irradiation has been tried by some as a means of reducing corticotrophin production. The results have been variable and, on the whole, disappointing (Sosman, 1949; Cope and Raker, 1955; Skrimshire, 1955; Dohan, Raventos, Boucot, and Rose, 1957). It is, therefore, an unsatisfactory method of therapy, and in the absence of direct evidence of a primary pituitary fault, its rationale remains uncertain. The same may be said of surgical removal or electrocoagulation of the pituitary, although both are capable of inducing a remission (Luft, Olivecrona, Ikkos, and Hernberg, 1957).

Because of the serious and progressive nature of the disease, surgeons have turned their attention to a direct attack on the adrenal glands. Early attempts at extensive resection of adrenal tissue were hazardous and few patients survived operation. More recently, however, the availability of cortisone and hydrocortisone has made adrenalectomy relatively safe, and this operation now offers the patient with Cushing's syndrome the best prospect of return to normal life (Poutasse and Higgins, 1953; Sprague, Kvale, and Priestley, 1953; Bishop, Glover, de Mowbray, and Thorne, 1954; Beck, Montgomery, and Welbourn, 1954; Cope and Raker, 1955; Skanse, Gydell, Wulff, and Koch, 1956). All agree that an adrenal tumour should be removed, but when, as in the majority of cases of Cushing's syndrome, there is hyperplasia or simple hyperfunction of the adrenal cortex, opinion is divided as to how extensive the adrenalectomy should be. Forsham and Thorn (1955) advocate total removal of both adrenal glands followed by lifelong substitution with cortisone, believing that recurrences are thereby prevented, and that cortisone replacement is a more satisfactory guarantee against the varying stresses of life than is the small piece of adrenal gland remaining after sub-total adrenalectomy. Those who perform subtotal resection remove either the greater part of each gland (Cope and Raker, 1955) or the whole of one and most of the other (Sprague and others, 1953; Beck and others, 1954; Skanse and others, 1956). They believe that a significant and satisfactory remission is obtained in all cases, that the majority of patients become independent of cortisone replacement, and that the recurrence rate is probably not greater than 10 per cent (Sprague, 1956).

Our purpose here is to record our experience in the diagnosis and treatment of 13 cases of Cushing's syndrome, to discuss certain aspects of the pre- and post-operative management, and to describe the patients' response to treatment.

CLINICAL FEATURES

The main clinical features of each patient in this series are listed in *Table I*. We shall not describe them in detail, since Cushing's syndrome is already well known (*Fig.* 168), but shall discuss certain aspects.

* More accurately 17-21-dihydroxy-20 ketosteroids. We are using the shorter term throughout for brevity.

Table I.—Main Clinical Features in 13 Cases of Cushing's S

Case No.	Sex	Age (years)	Length of History (years)	Special Clinical Features	Mean Blood-pressure (mm. Hg)		Dates of Operation	Side, Weight, Estimated Pre-operative Adrenal Tissue
					Before Operation	After Operation		
1	M.	21	1	Hypokalæmic alkalosis, severe osteoporosis (pathological fracture of spine), enlarged sella turcica, malignant retinopathy, muscular wasting, severe striæ	170/140	115/80	June 28, 19.. July 16, 19..	— —
2	F.	38	5	Streptococcal bacteræmia, striking alteration in colour of hair from blonde to brunette, amenorrhœa	180/130	150/100	Aug. 4, 19.. Aug. 18, 19..	7 14
3	F.	26	1	Depression, mental instability, amenorrhœa, minor increase in body hair growth	170/105	130/85	Oct. 6, 19.. Oct. 27, 19..	6 6
4	F.	19	1½	Pulmonary tuberculosis, severe osteoporosis, enlarged sella turcica, glycosuria, severe striæ, amenorrhœa	170/130	115/80	Jan. 5, 19.. Jan. 26, 19..	8 8
5	M.	50	3	Hypokalæmic alkalosis, thirst, polyuria, sweating, muscle wasting and weakness, malignant retinopathy, impotence, no striæ, severe ischæmic heart disease	230/140	200/100	May 20, 19.. June 22, 19..	4 9
6	F.	40	11	Malignant retinopathy, severe ischæmic heart disease, muscular wasting, amenorrhœa	235/140	150/100	June 22, 19.. July 9, 19..	6 7
7	F.	15	5	Early onset, menstruation delayed, no striæ, minor increase in body hair growth	160/100	130/80	Oct. 1, 19.. Oct. 12, 19..	4 6
8	F.	25	5	Malignant hypertension with retinopathy and spontaneous partial remission 3 yr. before, marked hirsutism, irregular and scanty periods	175/130	135/100	Oct. 5, 19.. Oct. 28, 19..	7 7
9	F.	45	2½	No striæ, occasional missed periods but no amenorrhœa, abscess of foot	175/120	140/100	Dec. 28, 19..	13 (Tu
10	F.	53	4	Muscular wasting, glycosuria, minor increase in body hair growth	200/115	130/90	April 19, 19.. May 17, 19..	9 6
11	F.	43	1½	Marked hirsutism, glycosuria, amenorrhœa	170/120	120/80	Aug. 9, 19.. Aug. 23, 19..	9 2
12	F.	43	1½	Marked hirsutism, menorrhagia, hypokalæmic alkalosis, muscular wasting	210/120	155/100	Oct. 11, 19.. Nov. 1, 19..	7 1
13	F.	48	4	Marked hirsutism, hypokalæmic alkalosis, pronounced purpura, severe osteoporosis (pathological fracture of spine), muscular wasting, glycosuria, severe striæ	210/115	—	May 22, 19.. June 12, 19..	

There were 11 women and 2 men in the series, giving a female preponderance of over 5 : 1. The average age of onset of the disease was 31 years with extremes of 11 and 49, and the age at operation varied from 15 to 53 years. The duration of symptoms before treatment was undertaken averaged 3 years and 8 months, the shortest being 1 and the longest 11 years. This lapse of nearly 4 years before the patients were referred for diagnosis seems unduly long in a condition so distinctive as Cushing's syndrome. It may be explained partly by the practitioners' unfamiliarity with such a rare condition and partly by the difficulty of distinguishing the early case, without florid signs, from the normal or hypertensive obese female.

Nevertheless, early diagnosis and treatment are of great importance, particularly in older patients, if crippling cardiovascular complications are to be avoided; and these can only be achieved by clinical awareness of the disease and careful assessment of suspected cases.

Hypertension was present in all cases and severe in 11 (*Fig.* 169). Four cases (*Cases* 1, 5, 6, and 8) had malignant retinal changes and a diastolic blood-pressure of 140 mm. Hg or more. Two patients (*Cases* 5 and 6), aged 50 and 40 years respectively, also had well marked hypertensive heart disease with cardiac enlargement, gallop rhythm, and severe myocardial ischæmia. Another (*Case* 8), a female of 25, had had malignant retinopathy and severe hypertension three years before we saw her. Following a partial remission the retinopathy had healed, but the blood-pressure was still high at the time of adrenalectomy.

Osteoporosis was severe in 3 patients. In 2 (*Cases* 1 and 13) the presenting symptom was pain

13 CASES OF CUSHING'S SYNDROME BEFORE AND AFTER ADRENALECTOMY

DATES OF OPERATION	SIDE, WEIGHT (in g.) AND ESTIMATED PROPORTION OF ADRENAL TISSUE RESECTED		DURATION OF FOLLOW-UP	SPECIAL FEATURES OF POST-OPERATIVE COURSE AND LONG-TERM FOLLOW-UP	DURATION OF CORTISONE-REPLACEMENT THERAPY
		(per cent)			
ne 28, 19..	—	85	4 yr.	Severe cortisone withdrawal symptoms with anuria—immediate response to cortisone. Long-term result excellent	2 wk.
ly 16, 19..	—	100			
ug. 4, 19..	7·5	95	3 yr., 11 mth.	Hysterectomy for menorrhagia and fibroids 16 mth. after adrenalectomy. Excision of eye 24 mth. after adrenalectomy. Temporary cortisone cover given for both operations	9 mth.
g. 18, 19..	14·9	100			
ct. 6, 19..	6·2	95	3 yr., 9 mth.	Post-operative response to corticotrophin—no long-term cortisone replacement given. Active pulmonary tuberculosis right lung 2 yr. after operation. Satisfactory response to chemotherapy and sanatorium treatment	Nil
ct. 27, 19..	6·6	100			
an. 5, 19..	8·1	95	3 yr., 6 mth.	Acute peripheral circulatory failure following second stage, response to I.V. noradrenaline	6 mth.
n. 26, 19..	8·2	100			
ay 20, 19..	4·3	90	4 mth.	Died of congestive heart failure 4 mth. after operation. Features of Cushing's syndrome had regressed	2 wk.
ne 22, 19..	9·5	100			
ne 22, 19..	6·9	95	5 mth.	Inadequate post-operative cortisone replacement due to patient's lack of co-operation. Acute adrenal failure treated in another hospital. Sudden death 5 mth. after adrenalectomy. ? acute crisis or cardiac death. Features of Cushing's syndrome regressing	Irregularly until death
ly 9, 19..	7·4	100			
ct. 1, 19..	4·7	90	2 yr., 9 mth.	Peripheral circulatory failure following first-stage adrenalectomy. Profound Addisonian pigmentation occurring 1½ yr. after operation	6 wk. initially. Restarted cortisone 26 mth. following adrenalectomy
ct. 12, 19..	6·9	100			
ct. 5, 19..	7·1	90	2 yr., 9 mth.	Incomplete regression of hirsutism—mild pigmentation of scars and pressure points	2 mth.
t. 28, 19..	7·7	100			
c. 28, 19..	13·0 (Tumour)	+ 95	2 yr., 7 mth.	Acute peripheral circulatory failure following operation—no pre-operative cortisone given. Pigmentation of operation scar for 1 yr., now faded. Minor post-operative 'rheumatic' pains	4 mth.
ril 19, 19..	5·5	95	2 yr., 2 mth.	Immediate mild post-operative hypo-adrenalism. Marked weight-loss of 28 lb. after 9 mth.; later treated with high protein diet and methylandrostenediol, following which adrenal crisis occurred necessitating intravenous hydrocortisone and noradrenaline	5 mth. initially. Permanent cortisone replacement 13 mth. following adrenalectomy
ay 17, 19..	6·4	100			
g. 9, 19..	9·0	95	1 yr., 11 mth.	Severe post-operative 'rheumatic' pains with pronounced facial and bodily desquamation of skin. Considerable pigmentation and symptoms of hypo-adrenalism during initial withdrawal of cortisone	11 mth. initially. Permanent cortisone replacement 13 mth. following adrenalectomy
g. 23, 19..	2·6	100			
t. 11, 19..	7·5	95	1 yr., 8 mth.	Hypotension following both operations necessitating hydrocortisone and noradrenaline. Salt deficiency after second operation necessitating 10 per cent saline. Post-operative course complicated by gastric volvulus necessitating operation. Considerable post-operative nausea and vomiting despite adequate and continuous cortisone replacement. Troublesome post-operative 'rheumatic pains'	Continuous cortisone replacement up to time of review
ov. 1, 19..	8·0	100			
ay 22, 19..	6·5	90	—	Uneventful recovery following first stage; 36 hr. following second stage peripheral circulatory failure occurred, treated with hydrocortisone and noradrenaline; B.P. response satisfactory, but patient became comatose and died 42 hr. after operation	—
ne 12, 19..	9·0	100			

in the back due to the collapse of several vertebral bodies. Of the remaining patients osteoporosis was mild or moderate in 4 and could not be detected clinically or radiologically in 6. In 2 patients a healed fracture was found in the rib which was resected at operation.

Hypokalæmic Alkalosis was a feature in 4 cases (*Cases* 1, 5, 12, and 13). In one (*Case* 5) it was associated with a raised serum sodium level, and thirst and polyuria were among the early symptoms. It was readily corrected by giving potassium chloride orally.

Muscular Wasting of the Limbs was a major finding in 6 patients (*Cases* 1, 5, 6, 10, 12, and 13) and was associated with hypokalæmia in 4. In one man aged 50 (*Case* 5) it reached such a severe degree that it prevented him from mounting stairs or handling tools efficiently.

Purple Cutaneous Striæ were found in 10 patients, but were absent in 3 (*Cases* 5, 7, and 9). They were most profuse in the younger man (*Case* 1), and extended to the wrists and ankles. Of the remaining 9 patients striæ were pronounced in 2 and relatively slight in 7. There was no definite correlation between the severity of the disease and the presence or degree of striæ.

Menstrual Irregularities were present in all 8 women who were menstruating before the onset of the disease. Two had minor irregularities with scanty loss and occasional missed periods, 5 had had amenorrhœa lasting for 1–5 years, and 1 (*Case* 12) had had menorrhagia for 2 months. Of the other 3 women, 1 (*Case* 7), whose symptoms pre-dated puberty, had not menstruated, 1 (*Case* 10) had had a normal menopause one year before the onset of her symptoms, and 1 (*Case* 13) had had a

hysterectomy for menorrhagia 4 years before she was seen.

Changes in Hair Growth and Alteration in Texture and Colour of Hair were common. Pronounced facial hirsutism (*Fig.* 170), alteration in pubic hair growth towards the male type, and increased growth of hair on the limbs were seen in 4 women (*Cases* 8, 11, 12, and 13). Less pronounced growth of hair on the body and limbs, without marked increase in facial hirsutism, was present in 3 other cases (*Cases* 3, 7, and 10). Changes in the texture and colour of the hair were noted in 3 women. One (*Case* 2), whose blonde hair had earned her the name of " Snowball ", became brunette over a period of 5 years.

FIG. 168.—*Case* 4. Typical appearance of patient with Cushing's syndrome. Note the round face, obesity of the trunk, kyphosis, ' buffalo hump ', acne, and purple cutaneous striæ.

FIG. 170.—*Case* 13. Facial hirsutism in Cushing's syndrome.

Infections were present in 3 patients. One (*Case* 2) had had severe paronychia, necessitating amputation of a finger, and a year later had developed streptococcal bacteræmia, which localized as a suppurative polyarthritis and unilateral panophthalmitis. Another (*Case* 4) had had bilateral active apical pulmonary tuberculosis which, in spite of a florid and advancing Cushing's syndrome, had healed satisfactorily during four months' treatment with chemotherapy in a sanatorium. A third (*Case* 9) had had a localized abscess of the left foot one month before admission.

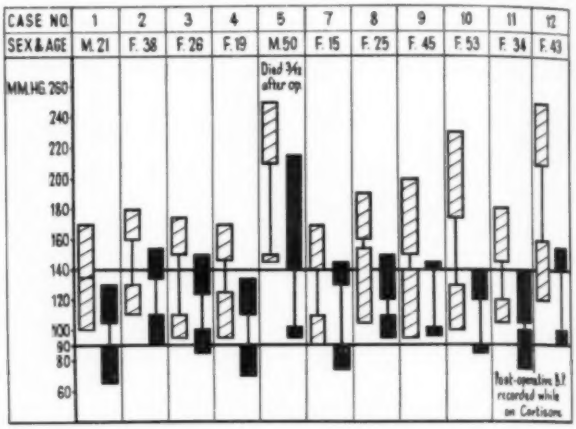


FIG. 169.—Blood-pressure in Cushing's syndrome before and after adrenalectomy. The systolic and diastolic ranges before operation are hatched in and those after operation are in black.

FIG. 171.—*Case* 5. Excessive wasting of muscles and absence of both striæ and obesity of trunk.

Blood Picture.—The hæmatological findings are recorded in *Table II*. Polycythæmia is a common but not constant finding in Cushing's syndrome and occurs in approximately 50 per cent of cases (Thompson and Eisenhardt, 1943). Red-cell counts were not done routinely in this series, but the hæmoglobin concentration was measured in all the patients. In 9 (*Cases* 2, 3, 4, 5, 7, 8, 10, 12, and 13) the hæmoglobin was 14·8 g. per 100 ml. (100 per cent Haldane) or more, and in 4 (*Cases* 3, 8, 10, and 13) it exceeded 16 g. The lowest reading was 13·3 g. per 100 ml. The total white-cell count was estimated in 10 patients and was above the upper limit of normal (Wintrobe, 1956) in 8. The findings in 1 (*Case* 2) were probably influenced by infection and are therefore excluded from the analysis. Of the remainder, 5 (*Cases* 4, 5, 7, 10, and 13) showed a neutrophil granulocytosis, 4 (*Cases* 8, 9, 12, and 13) an eosinopenia, and 3 (*Cases* 4, 5, and 12) a lymphopenia. Four patients (*Cases* 4, 5, 7, and 10) had a normal eosinophil count; 4 (*Cases* 7, 9, 10, and 13) had a normal lymphocyte count; while 1 (*Case* 8) had an absolute lymphocytosis. These findings are not entirely consistent with the usually accepted finding of eosinopenia and lymphopenia in Cushing's syndrome (Forsham and Thorn, 1955).

Disturbances in Carbohydrate Metabolism were present in 4 patients (*Cases* 4, 10, 11, and 13), that is, in 30 per cent, but were mild and consisted only of occasional glycosuria and slight elevation of the blood-sugar curve. No frank case of diabetes mellitus was encountered.

Gastric Secretion was measured in 9 patients and was increased in most (Kyle, Logan, Neill, and Welbourn, 1956). There was no evidence of peptic ulceration. After adrenalectomy the secretion was restored to normal.

Atypical Features.—In one patient only (*Case* 5) was it impossible to make a confident diagnosis on clinical grounds. He was a man of 50 years, who was nervous and apprehensive and had a hot flushed skin, pronounced sweating, tachycardia, ocular prominence, and tremor of the hands. Thirst and polyuria were early symptoms. Profound muscular weakness and wasting prevented him from working as a painter. While facial rounding and plethora were definite, the trunk was thin and wasted, and there were no cutaneous striæ (*Fig.* 171). Hypertension was severe and was associated with malignant retinopathy and gross myocardial ischæmia. The clinical picture suggested thyrotoxicosis, with associated myopathy, in addition to the Cushing's syndrome. The basal metabolic rate was + 37 per cent, but studies with radio-active iodine did not confirm over-activity of the thyroid gland. Biochemical features included a hypokalæmic alkalosis with mild hypernatræmia, while the excretion of glucocorticoids was very high (*Table III*). Radiography of the spine showed generalized osteoporosis of moderate degree. Thus the predominant clinical features were hypertension, profound muscular wasting, and weakness, and moderate osteoporosis, in contrast to the more usual florid obesity observed in Cushing's syndrome. In retrospect, we believe that some of the clinical

Table II.—Hæmatological Findings in 13 Cases of Cushing's Syndrome

Case No.	Sex	Hæmoglobin (g. per 100 ml.)	Leucocytes (per cu. mm.)					Remarks
			Total Count	Polymorphonuclears (normal* 3150-6200)	Eosinophils (normal* 50-250)	Lymphocytes (normal* 1500-3000)	Monocytes (normal* 285-500)	
1	M.	13·5	—	—	—	—	—	
2	F.	15·6	18,300	17,200	0	1100	—	Neutrophil granulocytosis, lymphopenia (suppurative arthritis of knee)
			12,800	—	—	—	—	Before operation (no infection)
3	F.	16·1	—	—	—	—	—	
4	F.	15·5	10,500	9555	105	630	210	Neutrophil granulocytosis, lymphopenia
5	M.	15·5	11,800	10,384	236	708	472	Neutrophil granulocytosis, lymphopenia
6	F.	14·2	14,600	—	—	—	—	Leucocytosis
7	F.	14·8	12,600	8694	126	2268	1512	Neutrophil granulocytosis, monocytosis
8	F.	16·6	11,800	6254	40	5034	472	Lymphocytosis, eosinopenia
9	F.	13·3	7620	4832	0	2402	386	Eosinopenia
10	F.	16·3	11,500	8165	115	2415	805	Neutrophil granulocytosis
11	F.	14·4	—	—	—	—	—	
12	F.	14·8	7100	5893	0	1207	—	Lymphopenia, eosinopenia
13	F.	16·2	13,200	10,692	0	2244	264	Neutrophil granulocytosis, eosinopenia

* After Wintrobe, 1956.

findings were in keeping with primary hyperaldosteronism, but the profound degree of protein breakdown, as shown by the muscular wasting, could have been due only to the increased circulating glucocorticoids. Two similar cases have been described recently by Melinger and Smith (1956), who point out that in rare cases considerable wasting of bone, muscle, and skin may replace obesity as the principal feature of the disease.

SPECIAL INVESTIGATIONS

Steroid Excretion.—Direct biochemical confirmation of the clinical diagnosis was sought in each case (*Table III*). The excretion of glucocorticoids was estimated in different ways at different times. In the first three patients the ' reducing corticoids ' (Broadbent, Newhouse, and Klyne, 1953) were measured, and the same investigation had been made in two later cases (*Cases* 9 and 10) before we saw them. The excretion was raised in all 5 patients (*Fig.* 172). This would, therefore, appear to be a valuable method of investigation, but theoretical objections led our biochemical colleagues to abandon it.

In the next group of patients the excretion of 17-hydroxycorticoids was estimated. In 1 (*Case* 3) it was done in the basal state only, and in 9 (*Cases* 4–12) it was also done following stimulation with 25 mg. of corticotrophin intravenously on two successive days (Reddy, Jenkins, and Thorn, 1952). Excretion (*Fig.* 173) was increased in the basal state and after stimulation in 6 patients (*Cases* 3–7 and 12) and was normal in 1 (*Case* 9). In 3 (*Cases* 8, 10, and 11) no basal excretion could be detected, but following stimulation the response in one (*Case* 3) was raised, that in another (*Case* 11) was greater than normal in view of the low initial reading, while the response in the third (*Case* 10) was sub-normal. There are reasons for supposing that the low readings which were obtained in some patients were the result of technical troubles with the method. They are difficult to account for otherwise, especially since higher levels were sometimes recorded after adrenalectomy (*Cases* 8 and 10) than before.

In the last patient (*Case* 13) we measured the 17-ketogenic steroids (Norymberski, Stubbs, and West, 1953) before and after stimulation with corticotrophin (Prunty, 1956). Six successive 24-hour collections of urine were made and from the third to the sixth day 20 clinical units of corticotrophin gel were injected intramuscularly twice daily. The first two days gave the basal excretion, while the remaining four showed the maximum response to stimulation. The basal level in this patient was high, but the rise after stimulation was not excessive. This patient was later found to have a basophil adenoma of the pituitary. The biochemical findings are consistent with spontaneous excessive secretion of corticotrophin and would account for the high basal steroid excretion and its lack of response to a relatively small dose of exogenous corticotrophin. We regard this test as the best available at present and now use it routinely.

Androgen excretion was measured in the form of 17-ketosteroids in 11 patients (*Fig.* 174), and the basal excretion was raised in 6.

Radiographic Investigation.—A special technique was used to demonstrate the adrenals in most cases (*Cases* 3–13). Retroperitoneal insufflation of oxygen, introduced by the presacral route, was combined with intravenous pyelography and tomography (Steinbach, Lyon, Smith, and Miller, 1952). The adrenals were outlined in most cases (*Fig.* 175), but it was not possible to detect minor degrees of hyperplasia. The area of the left adrenal shadow in the patient with an adenoma (*Case* 9) was greater than in any other case, but the tumour was not recognized pre-operatively. When the films were

Table III.—ASSESSMENT OF ADRENOCORTICAL FUNCTION IN 13 CA

CASE NO.	BEFORE OPERATION							AFTER ADRENALECTOMY: ISOLATED BASAL READINGS				
		17-*Hydroxycorticoids*			17-*Ketosteroids*	17-*Ketogenic Steroids*		17-*Hydroxycorticoids*		17-*Ketosteroids*		
	Reducing Steroids	Basal	ACTH Stimulation		Basal	Basal	After ACTH (two Highest Readings)	Soon after Stopping Cortisone	Subsequent Estimations at Intervals	Soon after Stopping Cortisone	Subsequent Estimations at Intervals	Years after Operation
			Day 1	Day 2								
1	4·7 6·4	—	—	—	34·4	—	—	0·0	6·3, 3·9	—	1·9	3 yr., 9
2	5·3	—	—	—	36·4	—	—	0·0	0·0, 15·5, 6·3	—	2·5, 5·1	3 yr., 6
3	4·0	14·4	—	—	10·6	—	—	0·0	1·7, 7·8	—	5·4	3 yr., 3
4	—	38·7	63·5	—	25·6	—	—	2·1	10·8, 7·0, 5·6	—	2·6, 5·1	3 yr., 3
5	—	34·4	60·9	85·8	13·8	—	—	—	—	—	—	—
6	—	14·2	44·2	32·2	—	—	—	2·2	—	—	—	—
7	—	26·9	52·7	—	—	—	—	0·0	3·1	—	3·3	2 yr., 2
8	—	0·0	33·8	43·0	21·8 31·0	—	—	2·6	0·0	1·9	3·5	2 yr., 5
9	3·2	8·8	20·5	—	6·8	—	—	—	6·6	1·7	6·5	2 yr., 3
10	8·2 4·7	0·0	5·4	—	9·0	—	—	1·9	—	—	—	1 yr., 8
11	—	0·0	21·4	22·2	19·9	—	—	—	—	—	—	1 yr., 2
12	—	12·2	44·6	50·0	7·1	—	—	—	—	—	—	—
13	—	—	—	—	19·2	36·6 44·2	43·5 52·0	—	—	—	—	—

* All figures represent mg. of steroids per

reviewed afterwards the tumour shadow was seen (*Fig.* 176), but similar shadows had been seen in other cases and had not proved significant.

continued to progress rapidly. Two others (*Cases* 9 and 10) were treated with testosterone before we saw them, but neither benefited from it.

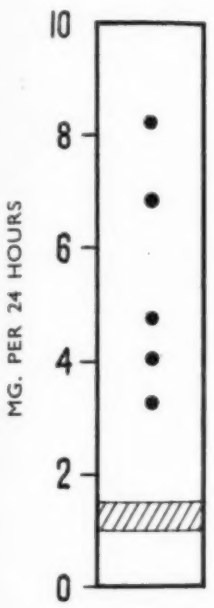


FIG. 172.—Excretion of reducing corticoids in 5 cases of Cushing's syndrome. (For details *see Table III* and text. Figures represent highest levels obtained in each patient.)

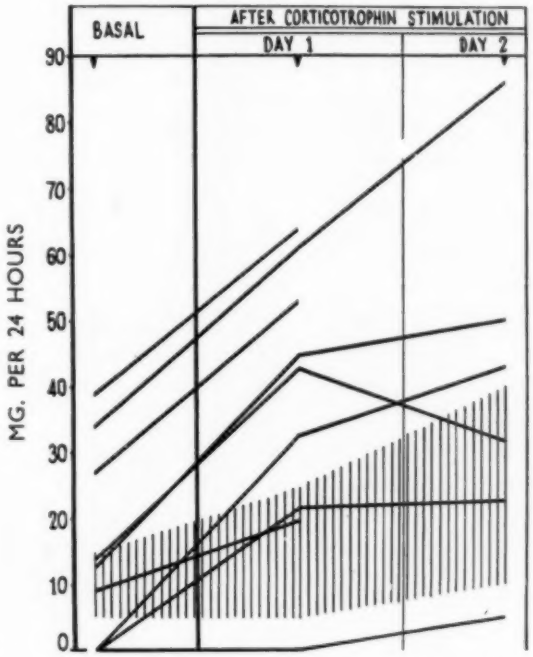


FIG. 173.—Excretion of 17-hydroxycorticoids in basal state and following stimulation with corticotrophin in 9 cases of Cushing's syndrome. (For details *see Table III* and text.)

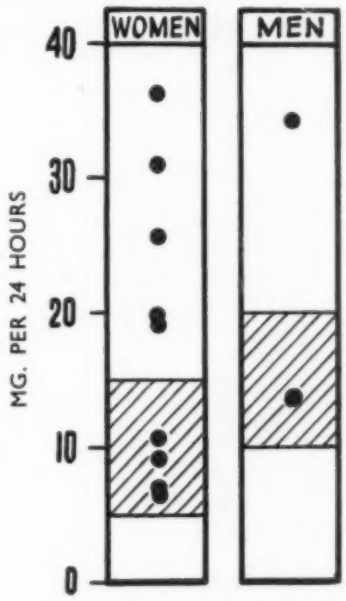


FIG. 174.—Excretion of 17-ketosteroids in 11 cases of Cushing's syndrome. (For details *see Table III* and text. Figures represent highest levels obtained in each patient.)

The shaded areas in *Figs.* 172, 173, 174, and 184 represent the ranges accepted as normal in the Royal Victoria Hospital laboratory.

SURGICAL THERAPY

Two patients (*Cases* 1 and 4) were treated initially by irradiation of the pituitary, but in both the disease

For these reasons, and because of the excellent results which had been achieved by others, we embarked on adrenalectomy as the primary form of

CUSHING'S SYNDROME BEFORE AND AFTER ADRENALECTOMY*

ADRENALECTOMY

ACTH STIMULATION TEST

Years after Operation	17-Ketogenic Steroids						17-Ketosteroids					
	Basal Excretion		Stimulated Excretion				Basal Excretion		Stimulated Excretion			
	Day 1	Day 2	Day 1	Day 2	Day 3	Day 4	Day 1	Day 2	Day 1	Day 2	Day 3	Day 4
3 yr., 9 mth.	7·4	2·2	4·7	2·8	6·9	13·9	11·7	10·2	9·0	6·0	9·1	10·6
3 yr., 6 mth.	10·1	6·7	9·3	8·3	11·4	13·4	7·0	5·4	6·3	5·4	8·5	6·8
3 yr., 3 mth.	5·9	2·4	4·6	8·3	5·9	7·3	5·6	3·0	3·3	4·0	4·2	5·0
3 yr., 3 mth.	5·3	12·0	12·5	15·3	16·3	8·9	4·7	2·7	4·9	3·9	3·5	1·3
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—
2 yr., 2 mth.	0·0	—	—	—	0·0	0·0	0·0	—	—	—	0·0	0·0
2 yr., 5 mth.	3·3	3·6	3·2	5·3	3·5	7·5	2·0	1·8	2·6	5·5	4·6	3·8
2 yr., 3 mth.	8·9	4·7	21·8	29·3	31·6	37·6	10·3	7·3	6·6	13·9	13·9	14·0
1 yr., 8 mth.	14·7	—	—	—	12·5	8·0	3·6	—	—	—	4·0	4·9
1 yr., 2 mth.	1·6	—	—	—	0·6	1·3	0·4	—	—	—	1·2	0·8
—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—

urs in urine—*see* text for details of methods.

treatment. We based our policy on that of the Mayo Clinic group (Priestley, Sprague, Walters, and Salassa, 1951 ; Sprague and others, 1953), whose experience of adrenalectomy for this condition is unrivalled. Briefly, the policy was to remove an adrenal tumour, if one was present, and to remove nine-tenths of one adrenal and all of the other when the glands were impracticable to inspect both before resecting one. Fortunately, though, the condition of both glands may be assessed fairly accurately by inspecting one, for hyperplasia is usually bilateral and the gland on the side opposite to a functioning tumour is usually atrophic. A small adrenal on one side does not *necessarily* denote a tumour on the other, however,

FIG. 175.—*Case* 13. Tomogram of adrenals outlined by oxygen, combined with intravenous pyelography.

FIG. 176.—*Case* 9. Radiograph showing adrenal adenoma (indicated by arrow). The stomach contains barium.

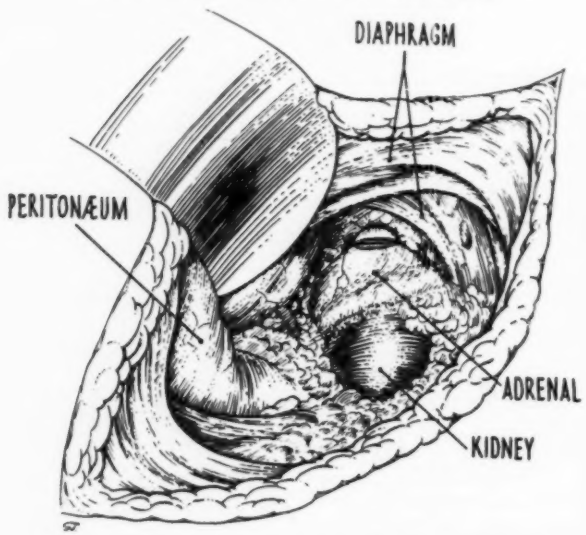


FIG. 177.—The crucial stage in left-sided sub-total adrenalectomy. The upper pole of the gland has been divided without disturbing its deep aspect.

hyperplastic or structurally normal. This policy was followed in 13 patients : an adenoma was removed from 1, and 12 underwent sub-total adrenalectomy. We hoped by these means to restore normal adrenal function and shall discuss later how far this hope has been achieved.

In none of our cases was a tumour located for certain before operation, and exploration of the adrenals was regarded as part of the investigation. The obesity in Cushing's syndrome renders the adrenals relatively inaccessible and makes it since in one of our cases without tumour (*Case* 11) one gland weighed only 2·6 g.

We prefer to operate on the left side first (unless there are signs of a tumour on the right) and did so in all but one (*Case* 1) of these cases. We found that operation was easier on the left side than on the right because the left gland is the more accessible and the easier to manipulate and remove sub-totally. When the critical sub-total resection has been accomplished on this side, the technically simpler total removal can be done on the right.

A fair amount of apparently normal tissue was found attached to the adenoma in *Case* 9. Since cortical tumours do not always secrete, we thought it wise to resect the gland sub-totally in addition to removing the tumour. Fortunately, a remission ensued and it was not necessary to explore the other side.

Operative Technique.—The two operations were done on separate occasions with an interval of 2–4 weeks between them. We approached the adrenal directly through a posterolateral incision with the patient on the side and the table well ' broken '. In our earlier cases we varied the site of the skin incision until we found the best level for it. On the left side, in all the later cases, the eleventh rib was resected extrapleurally (although the pleura was sometimes opened accidentally). The upper pole of the kidney is the best guide to the adrenal, which is often buried deeply in fat, and the orange colour of the gland distinguishes it clearly from the fat and from the tail of the pancreas. We tried various methods of sub-total resection, but found the following both simple and effective. The lateral and anterior aspects of the gland are cleared of fat,

without disturbing it posteriorly or injuring the small vessels which enter its periphery, and a small corner —not more than one-tenth of the whole—is selected to be left in the body. The upper pole is usually suitable and is severed from the main portion of the gland with scissors (*Fig.* 177). If it is viable its colour remains unchanged and blood oozes from its cut surface. If it becomes cyanosed and does not bleed the process is repeated with another corner. The remainder of the gland is then removed and the vein, which usually passes down from its medial aspect to the renal vein, is ligated and divided.

The right gland lies deeply behind the liver and is closely applied to the wall of the inferior vena cava. We found it best to approach it transpleurally through the bed of the tenth rib. The diaphragm is incised in the line of the skin incision and the gland, which is again found at the upper pole of the kidney, is cleared of fat on its anterior aspect. The short, treacherous adrenal vein, which enters the vena cava directly, is seen clearly in the centre of the operation field and is ligated and divided before the gland is removed.

The incisions were closed carefully, without drainage, but with interrupted sutures in all layers because of the real danger of break-down and infection of the wound. Penicillin was given for a few days post-operatively.

Substitution Therapy.—Cortisone and deoxycortone acetate were used according to the following scheme (*Table IV*).

Table IV.—Dosage of Cortisone and Deoxycortone Acetate before and after Adrenalectomy

Day	Cortisone Acetate	Deoxycortone Acetate
2 d. before operation	50 mg. 6-hourly, i.m.	
1 d. before operation	50 mg. 6-hourly, i.m.	
Day of operation	100 mg. 3 hr. before operation by mouth, 25 mg. 6-hourly, i.m.	10 mg. 3 hr. before and 5 mg. 6 hr. after operation, i.m.
1 d. after operation	25 mg. 6-hourly, by mouth if possible, otherwise i.m.	5 mg. 12-hourly, i.m.
2–5 d. after operation	25 mg. 6-hourly, by mouth if possible, otherwise i.m.	5 mg. i.m.
6–10 d. after operation	12·5 mg. 6-hourly by mouth	
11 + d. after operation	12·5 mg. b.d., by mouth	

Thereafter cortisone was withdrawn slowly, the necessary dosage being determined by the absence of signs of adrenal failure when trial reductions were made. The scheme had to be modified when signs of adrenal failure developed. Corticotrophin was given as well as cortisone for a period of two weeks in the patient who had a tumour (*Case* 9) with the object of stimulating the remaining adrenal.

The rapidity with which an adrenal crisis sometimes developed after operation led us to take two precautions. First, an intravenous drip, with a polythene tube passed well up the long saphenous vein, was started before the patient was taken to the theatre and provided a readily available route for the administration of hydrocortisone or noradrenaline. Secondly, the blood-pressure and pulse-rate were measured every 15 minutes after operation until they had remained stable for 2 days without specific intravenous therapy.

Initially, we took no special precautions with the first side except in one case (*Case* 5) whose excretion of glucocorticoids was very high and whose radiographs suggested the possibility of an adrenal tumour. However, we encountered an adrenal crisis after the first operation in 3 patients (*Cases* 7, 9, and 12), one of whom (*Case* 9) had a tumour which had not been recognized pre-operatively. We now give substitution therapy for both operations and withdraw it quickly after the first if no tumour is found and if adrenal failure does not develop.

Early Post-operative Complications.—There was one death shortly after the second operation, which will be described later. Significant wound infection developed four times, but resolved completely. There were minor chest complications on five occasions. One patient (*Case* 9) developed an acute depressive psychosis with paranoid features about two weeks after operation, but recovered completely within a few weeks.

Adrenal insufficiency, which was the commonest cause of post-operative death before the introduction of cortisone, is still to be feared. It was encountered in two acute forms, namely, peripheral circulatory failure and salt deficiency.

Acute Peripheral Circulatory Failure developed in 5 patients within thirty-six hours of operation. It followed the first stage only in 2 (*Cases* 7 and 9), the second stage only in 2 (*Cases* 4 and 13), and developed after both operations in 1 (*Case* 12). On three occasions (*Case* 12, both sides, and *Case* 13) it was not prevented by routine substitution therapy. This complication of adrenalectomy is rarely seen in patients with previously normal adrenal function (e.g., those with metastatic carcinoma of the breast), but its frequency and severity in patients with Cushing's syndrome cannot be over-emphasized. The clinical features of collapse, hypotension, and tachycardia are similar to those of oligæmic shock and often developed with alarming suddenness. In 4 patients noradrenaline was infused intravenously, with rapid restoration of the circulation, and this action was certainly life-saving. The fifth patient (*Case* 13), described in detail below, died in spite of an adequate response in the blood-pressure. Hydrocortisone was not available at the time we treated the first eleven patients. Our present practice, however, is to infuse 100 mg. of hydrocortisone in 500 ml. of 5 per cent glucose solution over a period of 4 hours if the systolic blood-pressure falls below 100 mm. Hg. If the fall in blood-pressure is profound, or if it continues after starting hydrocortisone, noradrenaline is given as well by means of a two-bottle transfusion set. A solution of 4 mg. in 500 ml. of normal saline is given as fast as necessary to restore the blood-pressure. The rate of infusion, which is adjusted every few minutes, must be reduced slowly and the noradrenaline can usually be discontinued within twenty-four hours. In one case (*Case* 12) superficial gangrene developed near the tip of the polythene catheter in the long saphenous vein. The slough separated and the ulcer healed without surgery. It remains to be seen whether any of the recent water-soluble steroids, such as hydrocortisone hemisuccinate, will render noradrenaline unnecessary.

Acute Salt Deficiency was seen in one patient (*Case* 12). It followed both operations, but was severe only after the second. Following the correction of acute peripheral circulatory failure the patient became apathetic, weak, and nauseated. In spite of adequate cortisone and deoxycortone cover, considerable salt deficiency occurred (serum sodium 117 mEq./l.) which was corrected by giving 10 per cent sodium chloride solution intravenously.

The danger of acute salt deficiency following adrenalectomy lies in its being mistaken for cortisone deficiency, for the symptoms of weakness, apathy, nausea, and vomiting are common to both states. While, in our experience, cortisone deficiency is much the commoner condition, the two states may occur together and salt deficiency, as in this case, may even be the predominant feature. The early recognition of salt deficiency is therefore important and it is our practice to carry out daily estimations of the serum electrolytes in the early post-operative phase to detect its occurrence. Minor degrees of deficiency can be corrected by giving salt by mouth and by using a more potent sodium-retaining substance such as 9-α-fluorohydrocortisone in addition to cortisone; but if serious sodium depletion occurs, immediate correction by intravenous sodium chloride is necessary.

Post-operative Death.—One patient (*Case* 13) died forty-two hours after operation on the second side. Recovery from the first operation three weeks previously had been uneventful. Her immediate post-operative condition was satisfactory, but thirty-six hours later her breathing became stertorous, the systolic blood-pressure fell rapidly to 70 mm. Hg, and she became difficult to rouse. Hydrocortisone was infused immediately without significant response, but when noradrenaline was added to the drip the blood-pressure was quickly restored and the systolic level kept at 110–120 mm. Hg. In spite of this the coma deepened and she died six hours later without regaining consciousness. Although there were no lateralizing signs it was thought that she had had an intracerebral vascular accident, but this was not confirmed at autopsy; and indeed no satisfactory explanation for her death could be found.

FINDINGS IN THE ADRENAL GLAND

The one adenoma (*Case* 9) was of the same colour as the adrenal cortex. It was ovoid in shape and measured 3·0 × 2·5 × 2·3 cm. The weight of the tumour together with the excised portion of the gland was 13·0 g. Histologically the adenoma had a well defined margin, but no definite capsule, and the cells were differentiated. The general structure resembled that of the normal zona reticularis.

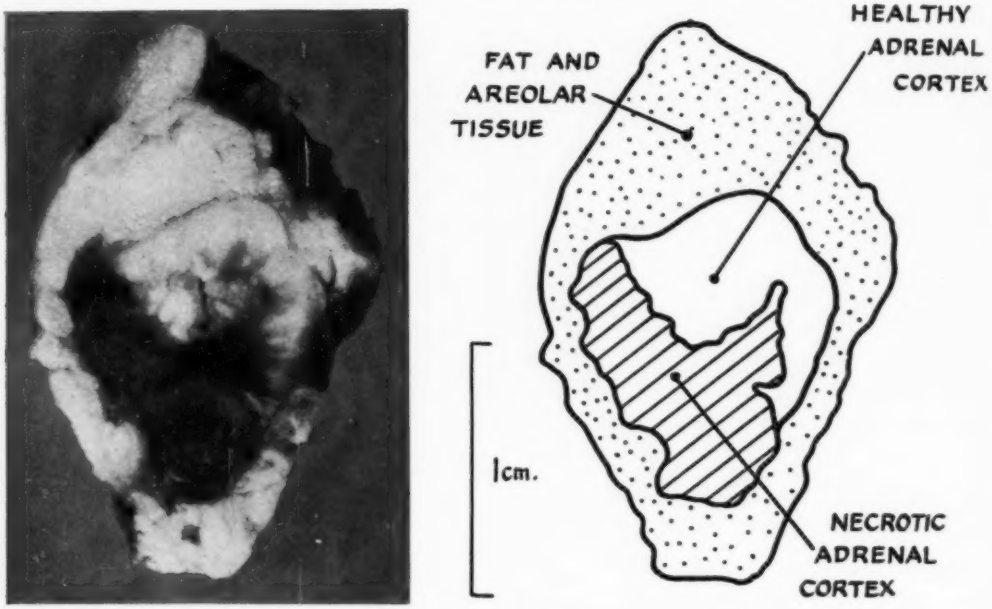


FIG. 178.—*Case* 13. Photograph of cut surface of adrenal remnant following sub-total resection.

The glands from the other 12 patients appeared grossly normal, apart from variations in size. The weights* varied from 2·6 g. to 14·9 g. (*Table I*), and in 3 cases one gland weighed more than twice the other. The average combined weight of the two glands was 15·2 g., which is nearly 30 per cent greater than normal (11·8 g.) and comparable with the weight of the adrenals in hypertensive subjects in general (Dawson, 1956). It is not, however, as great as that found in the Mayo Clinic series of patients with Cushing's syndrome (18·6 g., Sprague, 1953).

No portions of accessory cortical tissue (Cope and Raker, 1955) were found at operation, although a search was made for them in all cases.

Histologically the most striking feature was nodularity of the cortex (Sprague, 1953; Cope and Raker, 1955), which was seen in varying degrees in 10 of the 12 cases. In one (*Case* 2, right) there was a nodule 1 cm. in diameter. This nodularity, however, is seen in some normal glands and in many of

* *Case* 1 is excluded because the glands were not weighed. Ten per cent has been added to the weight of each left gland to allow for the estimated amount remaining in the body.

those of hypertensive subjects, and is not a specific feature (Fisher and Hewer, 1947; Dawson, 1956). The thickness of the cortex was increased in some, but not in all cases, and the most easily recognized zone was the reticularis. Special staining techniques were not used routinely.

The portion of gland left behind after sub-total adrenalectomy was examined in the patient (*Case* 13) who died after the second operation. The tip of the upper pole of the left gland was found and removed at autopsy. There was a pyramid of healthy tissue, whose base measured 1 cm. across, containing all layers of the cortex (*Fig.* 178). It weighed about 0·25 g. A portion of tissue of similar size, beneath the base of the pyramid, had undergone necrosis and contained hæmorrhagic areas.

The pituitary of this patient was examined also and contained a small basophil adenoma. We have no precise information about the pituitary in any other case.

LONG-TERM MANAGEMENT AND RESULTS

Two to three weeks after the second operation, when the wound had healed and all post-operative complications had subsided, the patient was convalescent and entered the long-term post-operative phase. The main problems of this period concerned the gradual withdrawal of cortisone and the detection and control of any signs of adrenal insufficiency which might develop.

Twelve patients survived operation and left hospital. Two of these, both of whom had severe

FIG. 179.—*Case* 4. Photograph of patient before, and 3 years after operation.

FIG. 180.—*Case* 11. Photograph of patient before, and 18 months after operation.

myocardial damage, died at home soon afterwards. One (*Case* 5) succumbed from cardiac failure after four months. The other (*Case* 6) left hospital too early, against our advice, and took cortisone irregularly. She was admitted later to another hospital in acute adrenal failure, but was treated effectively. She eventually died at home after five months, from either adrenal failure or coronary thrombosis. Neither of these patients was examined post mortem.

Effects of Adrenalectomy on the Disease Process.—Ten patients obtained remissions, and in each the process was complete within about six

FIG. 181.—*Case* 11. Scaly desquamation of skin post-operatively.

months. The facial and bodily appearance returned to normal (*Figs.* 179, 180), and all but one lost weight rapidly. This one (*Case* 7), a girl of 15, ate excessively and took little exercise. She became thinner in the face, but continued to increase in girth. Strict dieting subsequently restored her figure. The faces of some patients seemed to become excessively thin at first, but to return to normal later. Cutaneous striæ faded and left pale scars. Hair became fairer and softer in those in whom it had previously darkened, and facial hair diminished in most. Menstrual periods became normal in all but one of the women of child-bearing age. The exception was a patient with uterine fibroids (*Case* 2), who developed menorrhagia and was treated by hysterectomy. Recalcification of bones occurred slowly and backache persisted longer than other symptoms, but the pathological fractures healed and the deformities became stabilized eventually. The blood-pressure fell significantly in all cases (*Table I* and *Fig.* 169), and in 6 the diastolic pressure averaged 90 mg. Hg or lower. The two patients who died within six months of operation lost many features of their disease before death.

No sign of recurrence of Cushing's syndrome developed in any patient during the period of follow-up, which varied from one-and-a-half to four years.

Miscellaneous Effects of Adrenalectomy.—An invariable sign of improvement, and one which we came to regard as an index of adequate and successful surgery, was a striking change in the skin. It became dry, erythematous, and itchy and the superficial layers were shed in the form of fine dry scales (*Fig.* 181). The reaction varied in degree from transient itching and superficial scaling on the face, lasting a week or two, to pruritus and exfoliation

FIG. 182.—*Case* 9. Transient brown pigmentation of adrenalectomy scar.

involving the whole body and lasting much longer. It was least troublesome in those who rapidly achieved independence of cortisone, and was always aggravated when adrenal deficiency developed. We believe that desquamation continues until remission is complete and that signs of deficiency will always develop if cortisone is withdrawn completely before it has stopped.

Brown pigmentation appeared in the operation scars within a few weeks in 4 patients (*Fig.* 182). In 2 (*Cases* 8 and 9) it faded rapidly and was not accompanied by signs of adrenal failure. It was probably the result of a temporary 'rebound' phenomenon, whereby the pituitary secreted an excessive amount of melanocyte-stimulating hormone when the inhibitory effect of an excess of hydrocortisone had been removed by adrenalectomy. In the other 2 cases (*Cases* 7 and 11), which will be mentioned later, the pigmentation became widespread and was associated with other evidence of adrenal insufficiency.

Three patients (*Cases* 9, 11, and 12) suffered generalized rheumatic-like pains in the muscles and joints during the post-operative period. The pain was partly relieved by increasing the dose of cortisone and was most pronounced in the 2 patients (*Cases* 11 and 12) who showed the greatest initial dependence on it.

Administration and Withdrawal of Cortisone.—The necessary dosage of cortisone was

determined by the absence of signs of adrenal failure when trial reductions were made. The symptoms and signs of an inadequate dose were so constant, and they were relieved so regularly by cortisone, that we have used the term 'cortisone-withdrawal syndrome' to describe them (Beck and others, 1954). The syndrome is a sub-acute type of adrenal failure and must be expected in a mild form in most cases, since adjustment of the dose of cortisone is a matter of trial and error. In this series it developed at some time in 8 patients (*Cases* 1–5 and 10–12). The earliest symptoms were anorexia and nausea, which at first were noticed in the early morning and were aggravated by exercise and relieved by rest. Later they became persistent, and vomiting, bodily weakness, lethargy, apathy, abdominal discomfort, low-grade fever, and tachycardia followed. Hypotension was inconstant and never severe. In the first patient (*Case* 1), in whom treatment was delayed, there was a gradual reduction in the output of urine, culminating in anuria for thirty-six hours, and the mental state changed from one of ready co-operation to that of surly truculence. The facial desquamation, which is part of the process of remission in Cushing's syndrome, was invariably aggravated. Relief of symptoms and signs was afforded within a few hours by increasing the dose of cortisone. Corticotrophin was used in 4 patients (*Cases* 2–4 and 9), but was effective in only one (*Case* 3). Because of its inconstant effect and greater cost we now only use corticotrophin to stimulate an atrophic gland after removal of a tumour.

The rate at which the dosage of cortisone was reduced and the length of time during which it was required varied widely from one patient to another. Successful withdrawal over a period ranging from 2 weeks to 9 months was achieved in 5 (*Cases* 1, 2, 4, 8, and 9) and they have remained active and well, without clinical evidence of adrenal insufficiency, during the ensuing 2½–4 years. Two other patients (*Cases* 7 and 10) were without cortisone for periods of 2 years and 8 months respectively before signs of chronic adrenal insufficiency appeared. The former developed profound Addisonian pigmentation, without other symptoms (*Fig.* 183). The latter suffered excessive loss of weight, weakness, and anorexia and, while undergoing treatment in hospital with a high protein diet and methylandrostenediol (a 'non-virilizing' androgen), developed an adrenal crisis. Another patient (*Case* 11) developed generalized Addisonian pigmentation, without other symptoms of adrenal insufficiency, while still receiving cortisone. Eleven months after operation a cautious attempt was made to stop treatment, but the rapid appearance of 'cortisone-withdrawal' features made permanent therapy essential. We now regard pigmentation (in areas other than the operation scars) and excessive loss of weight as indications for continued cortisone replacement and do not wait for other symptoms and signs to appear. These patients with prolonged post-operative adrenal insufficiency (*Cases* 7, 10, and 11) have been adequately controlled with cortisone acetate by mouth and additional therapy (e.g., deoxycortone) has not been necessary. This agrees with our experience in the management of patients with Addison's disease (Beck and Montgomery, 1956).

In the remaining patient (*Case* 12) cortisone independence has never been achieved, and she has presented a difficult problem from many points of view. She has had the most stormy post-operative course of any patient in the series. She was the only one to develop acute adrenal failure after both operations, the only one to suffer acute salt deficiency, and the only one in whom noradrenaline caused

FIG. 183.—*Case* 7. Generalized Addisonian pigmentation following operation.

gangrene. Later, nausea and vomiting were persistent, despite a dose of cortisone which at times reached 100 mg. daily. The failure of this to control symptoms and the presence of normal serum electrolytes led to further investigation and the discovery of a gastric volvulus, of the organo-axial type, and paralysis of the left side of the diaphragm. These probably followed division of the phrenic nerve which had been undertaken twenty-one years previously for pulmonary tuberculosis. Three months after adrenalectomy about one-half of the central portion of the stomach was resected in the hope that the shortening would prevent rotation. There was some temporary benefit, but later sickness again became troublesome and was unrelieved by chlorpromazine or promezathine-8-chlorotheophyllinate (avomine). Fortunately the patient has maintained her weight. Repeated investigation has shown no evidence of adrenal insufficiency, and deoxycortone, in addition to cortisone, has had no effect. Although these symptoms followed adrenalectomy we do not think that the operation was responsible for them.

Adrenal Function.—The possibility that our patients might have an inadequate adrenocortical reserve, and therefore be unable to withstand stress, had concerned us from the outset and biochemical assessments of adrenal function had been made during the whole post-operative period. The basal 17-hydroxycorticoid and 17-ketosteroid excretions were measured at irregular intervals and showed

that the adrenocortical secretion was very low indeed immediately after stopping cortisone, but that in most cases it rose to low normal levels later (*Table III*). The experiences which we have just recorded concerning prolonged or delayed adrenal insufficiency led us to investigate adrenocortical function in detail

DISCUSSION

It is clear that the outlook for patients with Cushing's syndrome has changed completely since extensive adrenalectomy became a safe procedure. The only practicable alternative at present is surgical hypophysectomy or irradiation of the pituitary, but

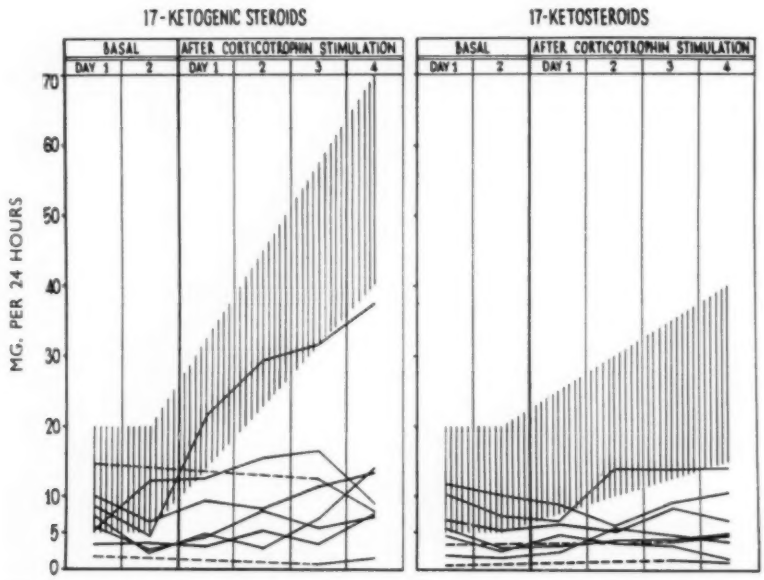


FIG. 184.—Post-operative assessment of adrenocortical function by measurement of steroid excretion in the basal state and following stimulation with corticotrophin. (For details *see Table III* and text.)

in the remaining patients. The effect of stimulation with corticotrophin for four days on the excretion of 17-ketogenic steroids and of 17-ketosteroids was measured in 8 patients after stopping cortisone and in one (*Case* 10) after she had restarted maintenance therapy. The time after operation at which this test was performed varied from fourteen to forty-five months. The results (*Table III* and *Fig.* 184) show that the only patient whose adrenal function approached normal was the one (*Case* 9) who had had a tumour removed and who still had one intact adrenal gland. The remainder excreted small or normal quantities of steroids in the basal state and showed little, if any, response to stimulation. These findings suggest that the small fragments of adrenal tissue which remained were working to capacity and that there was no functional reserve to allow them to respond to exogenous corticotrophin.

For this reason we have taken the precaution of supplying each patient with two cards (one to carry with him and one to keep at home), stating that he has undergone adrenalectomy, giving the required dosage of cortisone (if any), and advising an increase in the dose if he should develop signs of adrenal insufficiency or suffer stress in the form of infection, trauma, or a surgical operation. With the help of supportive therapy one patient (*Case* 2) withstood well, at separate times, a hysterectomy and excision of an eye, and another (*Case* 12), as already mentioned, underwent gastrectomy without trouble; a third (*Case* 3) developed active pulmonary tuberculosis two years after operation, but was cured by chemotherapy and sanatorium treatment. No supportive therapy was given and no signs of adrenal failure developed.

we believe that bilateral adrenalectomy, or removal of an adrenal tumour, is the treatment of choice in all except the rare cases in which a basophil adenoma is demonstrable. Our reasons for holding this view are these :—

1. The presence of an adrenal tumour cannot be excluded without adrenal exploration (as in *Case* 9 in our series). Valuable time may be lost if attention is directed first to the pituitary in a case of adrenal carcinoma.

2. Pituitary irradiation is uncertain in its effects and not without danger (Dohan and others, 1957).

3. Hypophysectomy causes hypothyroidism and loss of sexual function. The former can be treated. but the latter cannot. Adrenalectomy restores sexual function and fertility in those who were previously sterile.

The only point at issue (as we have indicated) is whether the adrenalectomy should be total or sub-total in extent. Our own experience of sub-total resection in 12 cases (omitting the patient with an adenoma) may be summarized as follows. One died post-operatively, and two more died within six months as a result (in one at least) of pre-existing cardiovascular disease. Nine underwent remission and have survived for periods between twenty months and four years. None shows any sign of recurrence. Five have stopped taking cortisone and remain in good health without it. Three others stopped cortisone for varying periods, but developed clinical signs of adrenal failure and had to restart it. One has never achieved independence of cortisone. Biochemical tests of adrenal function show that, while basal secretion is normal or low, the response

to corticotrophin is absent, or at best slight, in all. Our difficulty has not been, as we had anticipated, recurrence of the disease from enlargement of the remaining portion of adrenal gland, but rather the development of adrenal failure, following the withdrawal of cortisone, in patients whose adrenal function is inadequate.

Further experience may persuade us that it would be safer to perform total adrenalectomy and to accept the need for permanent cortisone replacement in all cases, but at present we prefer to persist in our policy of sub-total resection. The five patients who require no cortisone regard themselves as cured in a way that they would not if their lives depended on tablets, and we received ample warning of the development of adrenal failure (even if we failed to recognize it) in the three patients who had to return to cortisone therapy. We do *not* know what the effect would be of sudden severe stress in the form of major trauma or infection, but there is no reason to suppose that patients on maintenance doses of steroids would withstand it any better than those with a small endogenous supply. We would, however, urge certain precautions :—

1. The patient must be warned of the early symptoms of adrenal failure and should consult his doctor at once if he experiences them. He must also understand that intercurrent disease or trauma may necessitate taking cortisone temporarily and that, under such circumstances, he must tell his medical attendants at once that he has undergone adrenalectomy. The printed cards which we use embody this information and our patients are urged to carry them always.

2. The patient's doctor should be kept fully informed and be advised of the appropriate action in the face of actual or potential adrenal failure.

3. An accurate test of adrenocortical function (such as the 6-day test which we have used) should be performed soon after stopping cortisone.

4. The patient should be seen and assessed carefully at regular intervals.

It remains to be seen whether recurrence of Cushing's syndrome will develop later in any of the patients. It is clear that the recurrence rate varies directly with the amount of adrenal tissue which is left behind at operation and that it is highest in young subjects (Mason, 1957). Sprague and others (1953) indicate that "to insure a remission the resection must be almost extensive enough to give rise to adrenal insufficiency". Admittedly recurrence may not develop until some years after operation, but our findings suggest that the syndrome is most unlikely to return in many of our patients. Careful and prolonged study will be necessary before a final conclusion can be drawn.

SUMMARY

An account is given of the main clinical features and biochemical findings in 13 patients with Cushing's syndrome treated by adrenalectomy. One patient had a cortical adenoma removed with a sub-total resection of the adjacent gland, while the remaining 12, with cortical hyperplasia or hyperfunction, had nine-tenths of one adrenal and the whole of the other removed in two stages. Details of the operative technique and the pre- and post-operative treatment are given. The complications of adrenalectomy are described and the place of cortisone in their management is discussed.

Twelve patients survived operation and left hospital, while one died following the second stage of the adrenalectomy. Two patients succumbed after obtaining a partial remission, one four months after operation from cardiac failure, and the other five months after, from either acute adrenal insufficiency or a cardiac complication. Of the 10 patients alive, all have obtained a clinical remission without recurrence, and have been observed over periods of twenty months to four years. Continuous post-operative cortisone replacement has been necessary in one patient, and 3 have had to restart cortisone on account of signs of adrenal insufficiency. Five patients stopped cortisone successfully and continue in good health without it.

The effects of adrenalectomy in Cushing's syndrome are described and attention drawn to a skin change which is an invariable sign of improvement and a useful index of successful and adequate surgery.

Evidence of diminished functional adrenocortical reserve to exogenous corticotrophin was found in 7 patients tested after adrenalectomy, and the significance of this finding is discussed.

Reasons are given for the choice of bilateral sub-total adrenalectomy instead of total adrenalectomy in the management of patients with Cushing's syndrome without a tumour, but no final conclusion on the best method can be made without further experience and prolonged observation of the patients already treated.

Acknowledgements.—We are very grateful to the following for their help in this work: our colleagues, particularly Dr. R. S. Allison, Professor G. M. Bull, Dr. T. T. Fulton, Mr. T. L. Kennedy, Dr. J. S. Logan, Dr. J. F. Pantridge, Professor H. W. Rodgers, Dr. J. A. Smyth, Dr. P. E. R. Tattersall, and Dr. R. G. Vine, for referring patients to us; Dr. J. A. Smyth and Mr. D. Neill of the Royal Victoria Hospital Laboratory, and Dr. J. R. Doggart, Roche Research Fellow in Biochemistry in the Department of Surgery, Queen's University, for the biochemical investigations; Dr. R. N. Beck, formerly Principal Tutor in the Department of Medicine, Queen's University, who investigated the earlier cases with us; Dr. J. B. Gibson, Lecturer in Pathology, Queen's University, who reviewed the adrenal histology; Dr. M. G. Nelson, clinical pathologist to the Royal Victoria Hospital, for the hæmatology; Sir Frank Montgomery, Dr. D. C. Porter, Dr. J. J. McCavana, and Dr. P. N. Newsam of the Radiological Department of the Royal Victoria Hospital for the radiological investigations; Messrs. G. A Smith, R. G. Wood, and D. Mehaffy, A.R.P.S., for the diagrams and photographs; and Miss M. E. Beattie and Miss R. Orr for typing the script.

REFERENCES

ALBRIGHT, F., PARSON, W., and BLOOMBERG, E. (1941), *J. clin. Endocrin.*, **1**, 375.

BECK, R. N., and MONTGOMERY, D. A. D. (1956), *Brit. med. J.*, **2**, 921.

BECK, R. N., MONTGOMERY, D. A. D., and WELBOURN, R. B. (1954), *Lancet*, **2**, 1140.
BISHOP, P. M. F., GLOVER, F. N., DE MOWBRAY, R. R., and THORNE, M. G. (1954), *Ibid.*, **2**, 1137.
BROADBENT, I. E., NEWHOUSE, J. P., and KLYNE, W. (1953), *J. clin. Path.*, **6**, 190.
COPE, O., and RAKER, J. W. (1955), *New Engl. J. Med.*, **253**, 119, 165.
CUSHING, H. (1932), *Bull. Johns Hopk. Hosp.*, **50**, 137.
DAWSON, I. M. P. (1956), *J. Path. Bact.*, **72**, 393.
DOHAN, F. C., RAVENTOS, A., BOUCOT, M., and ROSE, E. (1957), *J. clin. Endocrin.*, **17**, 8.
FISHER, J. A., and HEWER, T. F. (1947), *J. Path. Bact.*, **59**, 605.
FORSHAM, P. H., and THORN, G. W. (1955), in *Textbook of Endocrinology* (ed. R. H. WILLIAMS), 2nd ed., 278, 282. Philadelphia: W. B. Saunders.
HERTZ, R., PITTMAN, J. A., and GRAFF, M. M. (1956), *J. clin. Endocrin.*, **16**, 705.
KYLE, J., LOGAN, J. S., NEILL, D. W., and WELBOURN, R. B. (1956), *Lancet*, **1**, 664.
LUFT, R., OLIVECRONA, H., IKKOS, D., and HERNBERG, C. A. (1957), *Acta endocr., Copenhagen*, **24**, 1.
MASON, S. (1957), *Proc. R. Soc. Med.*, in the press.
MELINGER, R. C., and SMITH, R. W. (1956), *J. clin. Endocrin.*, **16**, 350.
NORYMBERSKI, J. K., STUBBS, R. C., and WEST, H. F. (1953), *Lancet*, **1**, 1276.
POUTASSE, E. F., and HIGGINS, E. C. (1953), *J. Urol.*, **70**, 129.
PRIESTLEY, J. T., SPRAGUE, R. G., WALTERS, W., and SALASSA, R. M. (1951), *Ann. Surg.*, **134**, 464.
PRUNTY, F. T. G. (1956), *Brit. med. J.*, **2**, 615, 673.
REDDY, W. J., JENKINS, D., and THORN, G. W. (1952), *Metabolism*, **1**, 511.
SKANSE, B., GYDELL, K., WULFF, H. B., and KOCH, F. (1956), *Acta med. scand.*, **144**, 119.
SKRIMSHIRE, J. F. P. (1955), *Lancet*, **1**, 270.
SOSMAN, M. C. (1949), *Amer. J. Roentgenol.*, **62**, 1.
SPRAGUE, R. G. (1953), *Proc. R. Soc. Med.*, **46**, 1070.
— — (1956), personal communication.
— — KVALE, W. F., and PRIESTLEY, J. T. (1953), *J. Amer. med. Ass.*, **151**, 629.
STEINBACH, H. L., LYON, R. P., SMITH, D. R., and MILLER, E. R. (1952), *Radiology*, **59**, 167.
THOMPSON, K. W., and EISENHARDT, L. (1943), *J. clin. Endocrin.*, **3**, 445.
THORN, G. W., RENOLD, A. E., GOLDFIEN, A., NELSON, D. H., REDDY, W. J., and HERTZ, R. (1956), *New Engl. J. Med.*, **254**, 547.
WINTROBE, M. M. (1956), *Clinical Hæmatology*, 4th ed., 232. London: Kimpton.

FATAL DISSECTING ANEURYSM OF THE SPLENIC ARTERY

BY J. A. GILLESPIE AND W. GUTHRIE

FROM THE DEPARTMENTS OF SURGERY AND PATHOLOGY, QUEEN'S COLLEGE, UNIVERSITY OF ST. ANDREWS, DUNDEE

DISSECTING aneurysm of the splenic artery is a rare condition, only 3 cases specifically designated as dissecting aneurysm having been traced (Cosgrove, Watts, and Kaump, 1947; Shumway and Peyton, 1951; Soutar and Prain, 1951). All were fatal, and in none was a correct diagnosis made before autopsy. We present a further case with discussion of the clinical features and pathology.

CASE REPORT

A 60-year-old male was admitted to the Royal Infirmary, Dundee, on Oct. 13, 1955, with upper abdominal pain of two hours' duration. The pain, which began suddenly, had doubled him up and he became confused and incoherent. Three days previously he had taken to his bed with what he thought to be a flare-up of his ulcer symptoms. He had been treated for a duodenal ulcer for the past ten years, though he had never had a barium investigation.

ON EXAMINATION.—He was found to be confused and dyspnœic, with cyanosis of the lips and ear-tips, and a damp skin. The blood-pressure was 85/60, the pulse 96, and the temperature 96·0° F. There was marked upper abdominal rigidity and tenderness, and an absence of bowel sounds. A diagnosis was made of perforated peptic ulcer, perhaps complicated by hæmorrhage.

AT OPERATION.—The abdomen was opened by an upper right paramedian incision, and a small quantity of dark blood was seen free in the peritoneal cavity. The transverse mesocolon, the lesser omentum, and mesentery were widely infiltrated with blood, being greatly thickened. There was a large quantity of blood tracking behind the posterior parietal peritoneum from the diaphragm to the pelvis, particularly at the sides of the aorta, and extending towards the front on the left side as far as the anterior superior iliac spine. The lesser sac contained a few ml. of free blood, but its posterior wall was bulged forward by a large mass of blood-clot. There was anterior duodenal scarring from old peptic ulceration. The liver and spleen appeared to be normal; the stomach and bowel contained no obvious blood. A diagnosis of ruptured dissecting aortic aneurysm was made. During operation the patient's condition deteriorated greatly, and in spite of the rapid transfusion of 2 l. of blood and 1·5 l. of plasmosan he died a few hours later.

NECROPSY.—Examination was carried out nine hours after death. The hæmorrhage was found to come from a dissecting aneurysm of the splenic artery. The aneurysm began 2 cm. from the origin of the artery, extended along its length as far as its point of division into hilar and gastric branches, and also involved the major pancreatic branches. At its proximal end the aneurysm measured 11 mm. in diameter and the dissection had separated the adventitia from the media, compressing the lumen from above to convert it into a narrow slit 5 mm. long (*Fig.* 185). Near its middle the aneurysm wholly encircled the vessel wall. The artery was moderately tortuous, and its walls were sclerotic, being lined by an irregularly thickened intima showing no evidence of atheromatous degeneration.

On naked-eye examination no intimal tear was identified, but a site of communication between the aneurysmal cavity and the lumen proper was found in section of the main pancreatic branch of the splenic artery (*Fig.* 186). Hæmorrhage into the neck and body of the pancreas extended along the course of this artery, producing a striking separation of the pancreatic lobules by blood-clot and thrombus (*Fig.* 187), together with much bleeding around and into the wall of the splenic vein and its tributaries, which appeared otherwise healthy. The splenic hilum was filled with friable blood-clot, but the organ itself showed no abnormality.

Examination of the rest of the cardiovascular system revealed widespread arterial degeneration. The heart

(475 g.) showed concentric myocardial hypertrophy. The coronary arteries were arteriosclerotic with moderate atheroma, but there was no demonstrable occlusion. The aorta and its major abdominal and thoracic arteries showed severe atheroma, sclerosis, and calcification, but no aneurysm formation. The left kidney was of normal size, but showed on section old infarction atrophy of the anterior apical segment. The left renal artery was extremely atheromatous and sclerotic, and was the site of multiple aneurysms. The largest of these, involving the main trunk of the upper division of the artery, was saccular, measuring 15 × 12 × 10 mm., and was partially filled with thrombus. One of the smaller dilatations present on the further branches of this artery showed the

FIG. 185.—Section of dissecting aneurysm of splenic artery. Weigert-Sheridan Elastica/Hæmalum. (× 7·5.)

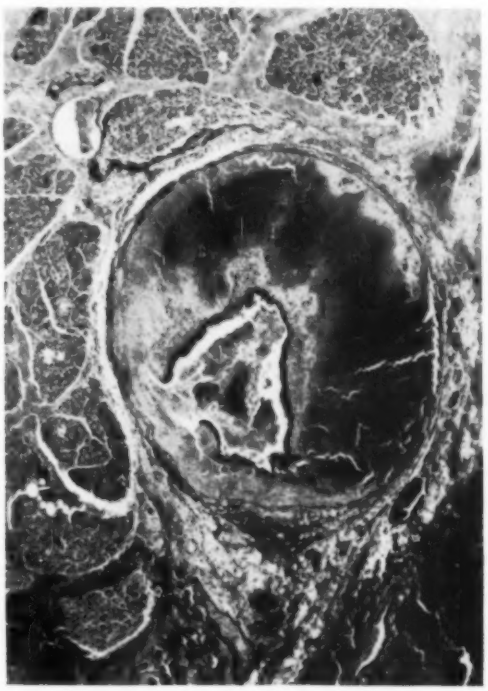


FIG. 186.—Section of major pancreatic branch of splenic artery showing communication between arterial lumen and aneurysm. Weigert-Sheridan Elastica/Hæmalum. (× 21.)

FIG. 187.—Dissecting aneurysm of splenic artery with hæmorrhage into pancreas. (× 1·5.)

FIG. 188.—Section of kidney showing dissecting renal artery aneurysm and parenchymatous atrophy. Weigert-Sheridan Elastica/Hæmalum. (× 10·5.)

naked-eye appearances of a dissecting aneurysm (*Fig.* 188). The right kidney was grossly enlarged (400 g.) and polycystic. Its artery was sclerotic, but showed rather less atheroma than the left.

Although the lower jaw and phalanges showed minimal acromegalic features the pituitary body seemed normal. No features of note were seen in the rest of the examination.

HISTOLOGY.—Sections of the splenic artery showed hypertrophy of the media with moderate replacement fibrosis, and proliferation and degeneration of the elastica, with minimal mucoid change. The intima was irregularly thickened by an increase in the fibrous tissue and proliferation of the elastic laminæ, but there was only scanty atheromatous degeneration in the thickened plaques. The proximal end of the aneurysm showed recent hæmorrhagic disruption of the outer part of the media, and a resulting separation of the adventitia; there was little histological evidence of repair. Lateral to this point laminated thrombus sealed a breach in the aneurysmal wall. Adventitial gaps with surrounding neutrophil infiltrate were noted in sections taken towards the middle of the aneurysm. Near the junction of the middle and lateral thirds of the splenic artery blood was seen issuing from a rupture in the aneurysmal wall causing destruction of the related pancreatic tissues. Sections from the middle of the aneurysm showed in places the greater thickness of the media to be torn from the internal elastic lamina. Irregular, partially necrotic fragments of media, with attached adventitia, formed part of the aneurysmal wall. Complete circumferential dissection was noted at this site.

The renal artery aneurysms occurred in areas of atheromatous degeneration superimposed on arteriosclerosis. The dissecting aneurysm resulted from the rupture of the wall of one of two arteries contained within a common sheath of outer elastica and adventitia which limited the aneurysmal dilatation. There was intense adventitial cellular reactions consisting mostly of plasma cells, many with Russell bodies. The smaller arteries of the kidney showed striking proliferation, up to ten elastica layers, and narrowing of the lumen, with related atherosclerotic 'hypertensive' nephropathy.

Comment on the Pathology.—The patient was clearly hypertensive and his arteries showed obvious atherosclerosis. In the reported cases of *saccular* aneurysm of the splenic artery the most significant accompanying abnormality described by Owens and Coffey (1953) is atherosclerosis. Of the other factors associated with aneurysm formation such as mycotic embolism, portal hypertension, congenital defect with associated arachnodactyly, pregnancy, trauma, or syphilis, there has been no evidence. Many sections were examined from the present case in an effort to show why and where the lesion began, but the hæmorrhage was so destructive that recognition of its site of origin was impossible. The absence of a gross intimal tear, the particular involvement of the outer media, and the presence of obliterative changes in the vasa vasorum, suggest that rupture of one or more of the latter vessels, with hæmatoma formation, was the primary lesion (Tyson, 1931). It is difficult to assess the importance of the focal medial degeneration seen in relation to the dissecting aneurysm. Such areas of necrosis, with loss of nuclear staining and fragmentation of elastica, could result from interference with the blood-supply by the dissection, especially if there has been some blood leakage prior to the major hæmorrhage, as in our case.

All four cases of dissecting splenic artery aneurysm have occurred in adults, with an average age of 59·5 years, and all showed arterial degeneration. Two of the patients were male and two female. The exact site of the aneurysm is different in each case, but rupture has resulted in profuse intraperitoneal and retroperitoneal hæmorrhage in all four. The spleen, usually enlarged in cases of saccular aneurysm, has been of normal size, weight, and appearance, apart from infarcts.

Aneurysms of the renal artery are not common, Silvis, Hughes, and Holmes (1956) having collected only 122 cases. In a comprehensive review of the literature up to 1951 Abeshouse mentions only one case of renal artery aneurysm associated with an aneurysm elsewhere, namely, in the aorta. It is rather surprising to note the low incidence of arterial degeneration in the reported cases of aneurysm of the renal artery (16 of 115 cases) especially as these aneurysms are commonest in the fifth and sixth decades.

DISCUSSION

The first two reported cases of dissecting aneurysm of the splenic artery were clinically rather different from Soutar and Prain's case and the present one, as in neither was an intra-abdominal lesion suspected before death.

The first patient (Cosgrove and others, 1947) was a 62-year-old man who complained of left intercostal pain six days after the wiring of a fractured mandible. He became lethargic, with marked physical weakness, and died in coma ten days later. A ruptured dissecting splenic artery aneurysm was found at necropsy. The second case (Shumway and Peyton, 1951), a 50-year-old woman, became unconscious at home while awaiting investigation for a suspected intracranial neoplasm. She was admitted to hospital in a semi-stuporous state. Three days later she suddenly became severely shocked and died. At no time was there any clinical indication of an abdominal lesion, although necropsy revealed a ruptured dissecting aneurysm of the splenic artery as well as an occipital meningioma.

Soutar and Prain's patient, a woman of 66, presented with pain in the left side of the chest and upper abdomen associated with nausea and vomiting. A coronary occlusion was at first suspected. Later, the presence of an acute abdominal lesion became more obvious and laparotomy was undertaken. About 1 litre of free blood was present in the abdominal cavity and there was a large quantity of retroperitoneal blood-clot in the region of the lesser sac. The bleeding-point was not found, but it was surmised to lie somewhere on the cœliac axis or one of its main branches. The patient's condition gradually deteriorated after operation, and she died a week later. Necropsy showed a dissecting aneurysm of the splenic artery.

The symptoms in this case, unlike those in the two previous cases, pointed to an abdominal lesion, and the operative findings were very similar to those in our own case. It is interesting to compare the clinical features of these two cases with those reported in *saccular* aneurysm of the splenic artery.

While dissecting aneurysm is rare, saccular aneurysm of the splenic artery has been reported 246 times. Most of these cases have been considered in two extensive reviews (Sherlock and Learmonth, 1942; Owens and Coffey, 1953), and more recently by Hill and Inglis (1955). The unruptured saccular aneurysm, by virtue of its bulk, may give rise to a number of signs: a palpable and perhaps pulsatile tumour; an audible systolic bruit in the upper abdomen; radiological evidence of calcium in the aneurysmal wall; pulsatile indentation of the

stomach on barium-meal examination; a filling shadow on aortography.

A saccular aneurysm may thus be diagnosed, on occasion, before the sac ruptures. A dissecting aneurysm, however, is unlikely to give rise to symptoms until the blood has burst outside the vessel. When this occurs, the picture is similar to that of rupture of a saccular splenic artery aneurysm. The two cardinal clinical features are now seen, severe upper abdominal pain, perhaps more marked in the left upper quadrant or left side of the chest, and profound shock. Perforation of a peptic ulcer, or acute pancreatitis, seems the likely diagnosis. Another feature not uncommonly seen in ruptured saccular splenic artery aneurysms, as also in our case of dissecting aneurysm, is the story of 'double rupture', a slight pain, presumably from blood leakage, preceding by two or three days the onset of severe pain due to the major hæmorrhage.

The main reason for the publication of this paper is to draw attention to a condition which is uniformly fatal if unrecognized. Ruptured splenic artery aneurysm might well be considered if an adult presents with sudden and severe upper abdominal pain in association with great shock, especially if there be a story suggestive of double rupture. When, at laparotomy, the surgeon finds a large amount of retroperitoneal blood-clot in the region of the lesser sac the splenic artery should be explored. If an aneurysm is present the vessel may be ligated and splenectomy carried out. It may be difficult, however, especially in dissecting aneurysm, to identify the vessel in the large mass of blood-clot.

Both Soutar and Prain's patient and our own might have been saved by immediate splenic artery ligation had the possibility of splenic artery aneurysm been in mind, though in our case the related disease in the renal artery would have rendered long-term survival unlikely.

SUMMARY

1. A fatal case is reported of ruptured dissecting aneurysm of the splenic artery, with unruptured aneurysms of the left renal artery.

2. The clinical features and pathology have been discussed.

3. Only two previous reported cases, and one unreported case, of dissecting aneurysm of the splenic artery have been traced.

4. All four cases were fatal. In none was a correct diagnosis made either before, or at, laparotomy.

Note.—Since submitting this paper for publication, an incidental necropsy finding of dissecting aneurysm of the splenic artery has been described by Watson (1956).

Acknowledgements.—We wish to record our thanks to Professor D. M. Douglas and Professor A. C. Lendrum for advice and criticism in the preparation of this paper; also to Mr. J. W. Corkhill and Mr. D. Fraser for technical assistance.

REFERENCES

ABESHOUSE, B. S. (1951), *Urol. cutan. Rev.*, **55**, 451.

COSGROVE, G. E., WATTS, J. C., and KAUMP, D. H. (1947), *Amer. J. Clin. Path.*, **17**, 372.

HILL, R. M., and INGLIS, A. (1955), *Brit. J. Surg.*, **42**, 408.

OWENS, J. C., and COFFEY, R. J. (1953), *Int. Abstr. Surg.*, **97**, 313.

SHERLOCK, S. P. V., and LEARMONTH, J. (1942), *Brit. J. Surg.*, **30**, 151.

SHUMWAY, N. E., and PEYTON, M. D. (1951), *Surgery*, **30**, 1012.

SILVIS, R., HUGHES, W. F., and HOLMES, F. H. (1956), *Amer. J. Surg.*, **91**, 339.

SOUTAR, S. F., and PRAIN, J. H. (1951), personal communication.

TYSON, M. D. (1931), *Amer. J. Path.*, **7**, 581.

WATSON, A. J. (1956), *J. Path. Bact.*, **72**, 439.

RECURRENCE AFTER RESECTION FOR BRONCHIECTASIS

By J. T. CHESTERMAN

FROM THE DEPARTMENT OF THORACIC SURGERY, CITY GENERAL HOSPITAL, SHEFFIELD

INTRODUCTION

THIS paper deals with the recurrence of dilatation after resection for bronchiectasis, not with the evolution of pre-existing unresected bronchiectatic areas. The reason for this paper is the lack of information on the subject, as the possibility of recurrence is now a major problem in advising for or against surgery in many cases. Previous papers (Chesterman, 1943, 1951, 1955 a, b) have dealt with the indications for surgery, the complications, and results. The basis of this communication comprises 245 consecutive cases involving 273 resections starting in the summer of 1945 when an official Thoracic Surgical Unit was opened at the City General Hospital, Sheffield, and the statistics refer to these cases, all of which have been followed up for at least three years. However, further information is drawn from all cases operated upon by me since 1938. The fallacy of this follow-up lies in the absence of post-operative bronchograms taken at least two years after resection in all patients, though these have been obtained in clinically suspicious cases.

The first two tables (*Tables I, II*) are inserted to show the main features in age, sex, type of operation, and pathology found in the series under review.

RECURRENT CASES FOLLOWING UNILATERAL SUBTOTAL RESECTION

Incidence.—There are 19 cases of recurrence in 203 such resections, making an incidence of 9 per cent. Further analysis, however, shows that there

is an increased tendency for recurrence in the earlier age groups: for instance, 7 cases are found under the age of 9 years and 12 cases under the age of 18 years, which makes an incidence of 12½ per cent and 10 per cent respectively of the cases operated upon up to those ages, and of 37 per cent and 63 per cent of the total recurrences.

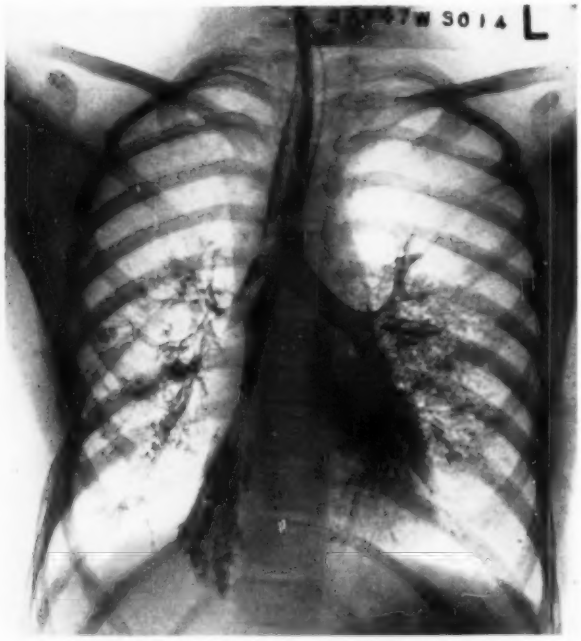


FIG. 189.—*Case* 12. Complete collapse of right middle lobe. Bronchogram 11 months after right lobe lobectomy.

Sex.—The sex distribution is not significant at any age.

Side of Recurrence.—Recurrence has always been on the operated side.

Type of Bronchiectasis.—Recurrent bronchiectasis is nearly always cystic in nature rather than cylindrical, whatever the cause may be. Details of recurrence in 19 cases are given in *Table III*.

Aetiology.—Four main causes are found :—

1. *Collapse.*—This may mean either airlessness (apneumatosis) or fibrosis leading to incomplete post-operative expansion of part or all of the remaining pulmonary tissue, so that the thoracic cavity is never completely filled by lung. Recurrence due to this cause appears within two years of the primary resection. Four cases (*Cases* 2, 8, 12, 17) developed bronchiectasis after apneumatosis and 8 cases (*Cases* 1, 7, 10, 13, 15, 16, 18, 19) from fibrosis which led to incomplete expansion (*Fig.* 189, *Table III*). A pleural effusion forms almost always in both types of collapse. It should be noted that the first type of collapse, if unrelieved, is always followed by bronchiectasis, though in the latter type only 50 per cent show recurrence.

2. *Chronic Infection in a Fully Expanded Lobe.*—This chronic infective process usually starts as a severe and prolonged 'cold' months or even years after resection. Radiography shows clouding of the lobe which progresses to a uniform opacity suggestive of consolidation before cystic areas gradually appear within it. The pathological process is that of a chronic infective œdema leading to fibrosis, a condition known as 'carnification' by the older morbid anatomists. Two such cases (*Cases* 11, 14) appeared in the present series. (*Figs.* 190, 191.)

Table I.—GENERAL STATISTICS

		Type of Operation	
Cases: 245. Male, 127; female, 118		Pneumonectomy	38
Age: 1 yr. 11 mth.–63 yr.		Unilateral subtotal resections	203
		Bilateral resections	24
		Resection in diffuse disease	8
		Pathology	
Resections: 273. Male, 143; female, 130		Cylindrical 2/3. Saccular 1/3.	
Time: 14 min.–3 hr.		The latter mainly in upper lobes almost always in post-operative recurrence, probably always in congenital cases and incomplete resolution of staphylococcal infections	
Sex: Distribution not significant at any age		Marked collapse present in 40 per cent of cases	

3. *Acute Necrotizing Infection.*—Such an infection may occur at any time after a resection, and occurred in 2 cases (*Cases* 3, 4). (*Figs.* 192, 193.) One followed a tonsillectomy three years later and the other also developed three years later, but the exact cause was not apparent. Both cases responded to further surgery for a short time, but both later died of acute, widespread tuberculosis, which did not respond to therapy. In neither case was there any evidence of tuberculosis at the time of operation or in the resected specimens.

4. *Post-operative Tuberculous Infection of the Pleura.*—Cases in which a recurrent pleural effusion or empyema occurs later nearly always prove to be of tuberculous origin, even though no evidence of tuberculosis is found clinically, at the operation, or in the resected specimen. This is essentially a chronic tuberculous involvement of the pleura, not of the parenchyma of the lung, and it leads to non-tuberculous fibrosis and bronchiectasis of the lobe. Three such cases occurred in this series (*Cases* 5, 6, 9) and all are improving after further surgery and

Table II.—RESECTIONS

Age	*Number of Cases*	*Area removed*			
1–10	67	Right lung	7	Left lung	31
11–20	81	Right upper lobe	11	Left upper lobe	14
21–30	69	Right middle lobe	19	Lingula	2
31–40	39	Right lower lobe	8	Left lower lobe	91
41–50	14	Right upper lobe and right middle lobe	2		
51–60	2	Right middle lobe and right lower lobe	22	Left lower lobe and lingula	35
61–70	1	Lobe and segments	7	Lobe and segments	5
		Segments	7	Segments	12
	273		83		190

Table III.—Recurrent Bronchiectasis in Unilateral Subtotal Resections of Lung

Case	Name	Number	Sex	Age First Operation	Operation	Date	Recurrence	Further Operation	Date	Result
1	S. T.	192597	M.	23	Left lower lobectomy	April 26, 1946	1 yr., incomplete expansion, infection	Left upper lobectomy	Sept. 18, 1948	Death. Acute abdomen March 31, 1949. Post-mortem, chest satisfactory
2	M. S.	189910	F.	17	Left lower lobectomy	Feb. 12, 1946	15 wk., complete collapse	Refused further surgery		Death. Bronchopneumonia, Aug., 1947
3	K. F.	52/7926	M.	4	Right middle and right lower lobectomy	Nov. 10 1947	Full expansion, 3 yr. later lung abscess after tonsil and adenoid operation	Right upper lobectomy. Tuberculous empyema	Dec. 15, 1951	Death. Acute tuberculosis, Oct., 1952
4	M. G.	56/5461	F.	28	Anterior segment right upper lobectomy	Sept. 20, 1948	Full expansion, 3 yr. later lung abscess. Right upper lobe drainage bronchiectasis	Right pneumonectomy. Tuberculous empyema	Feb. 1, 1954	Death. Acute tuberculosis, June, 1956
5	C. S.	52/1992	M.	22	Left lower lobectomy	June 19, 1945	1 yr., fistula and empyema sinus re-opened 1953. Tuberculosis + pleura	1. Closure fistula, lingulectomy 2. Left upper lobectomy	May 13, 1947 March 15, 1955	At work, small sinus present, Sept., 1956
6	R. O.	52/8349	F.	22	Left lower lobectomy	Oct. 2, 1951	6 wk., pleural effusion tracheobronchitis	Left upper lobectomy, empyema	Nov. 27, 1951	Pleural tuberculosis + found Feb. 27, 1952. Small sinus, doing housework, Aug., 1956
7	H. T.	53/19387	M.	35	Left upper lobectomy	April 22, 1947	2 yr., incomplete expansion to clavicle only	Left lower lobectomy, empyema	April 27, 1950	Worked till Easter, 1953. Death. Cor pulmonale Aug. 18, 1953
8	S. W.	52/3848	F.	3	Left lower lobectomy	April 11, 1950	Pertussis after operation and collapse left upper lobe	Left upper lobectomy	Jan. 29, 1951	Satisfactory at present time
9	D. B.	52/8492	F.	21	Right lower lobectomy (anaesthetic difficulties)	Oct. 29, 1949	Complete collapse, recurrent empyemata	1. Right middle lobectomy 2. Right upper lobectomy	Jan. 6, 1950 May 7, 1953	Pleural tuberculosis + found Jan. 23, 1956. Healed, July, 1957
10	A. B.	52/6836	F.	14	Left lower lobectomy and lingulectomy	Nov. 30, 1948	3 mth. incomplete expansion	Left upper lobectomy	June 2, 1949	Some scoliosis. At work, Oct., 1956
11	D. M.	52/6677	M.	16	Left lower lobectomy	June 26, 1945	Full expansion, 1952 'pneumonitis'	Left upper lobectomy, empyema	Sept. 19, 1952 July 20, 1953	Sinus. At work, Oct., 1956 Pleural tuberculosis found Oct. 3, 1956
12	D. B.	52/9950	F.	6	Right lower lobectomy	March 13, 1946	Collapse right middle lobe	Right middle lobectomy	April 21, 1947	Satisfactory at present time
13	E. Y.	52/3543	M.	8	Left lower lobectomy and lingulectomy	May 25, 1948	4 mth. incomplete expansion	Left upper lobectomy	Feb. 3, 1949	Satisfactory at present time
14	W. R.	52/126	M.	11	Left lower lobectomy	Sept. 20, 1948	Full expansion, 1949 'pneumonitis'	Left upper lobectomy	June 1, 1950	Satisfactory at present time
15	W. G.	52/5457	F.	22	Left lower lobectomy	Sept. 23, 1950	Incomplete expansion, fluid, tracheobronchitis	Left upper lobectomy	Oct. 26, 1950	Satisfactory at present time
16	J. H.	52/864	M.	16	Left lower lobectomy and lingulectomy	Oct. 29, 1951	Incomplete expansion, fluid, tracheobronchitis	Left upper lobectomy	Dec. 10, 1951	Satisfactory at present time
17	D. P.	53/15351	F.	5	Left lower lobectomy	June 9, 1953	Collapse, fluid, tracheobronchitis	1. Decortication 2. Left upper lobectomy	July 7, 1953 Nov. 30, 1954	Satisfactory at present time
18	P. H.	53/15579	M.	5	Left lower lobectomy and lingulectomy	Feb. 24, 1953	Incomplete expansion, fluid, tracheobronchitis	Left upper lobectomy	April 21, 1953	Satisfactory at present time
19	S. D.	52/10896	F.	4	Anterior segment right upper lobectomy and right middle lobectomy	Nov. 8, 1952	Incomplete expansion, right lower lobe	Right lower lobectomy	June 12, 1956	Satisfactory at present time

antibiotic treatment, and are leading practically normal lives save for a sinus in the chest wall in two.

Treatment and Results.—All patients were offered further surgery, which was accepted in 18 of the 19 cases; the one who refused (*Case* 2) died later of bronchopneumonia.

Prevention.—Prevention lies in the selection of cases for operation (Chesterman, 1955 a), in the operation itself, and in the post-operative treatment. In the selection of cases there must be very strong reasons for operating on children with allergic manifestations or gross deformity of the chest wall. A pre-operative suspicion that fibrosis is present in the non-bronchiectatic areas is suggested by a history of recurring respiratory infection not localized to the grossly diseased area, by the retention of iodized oil in the lung for long periods, by relatively inadequate movement of the lung on X-ray screening,

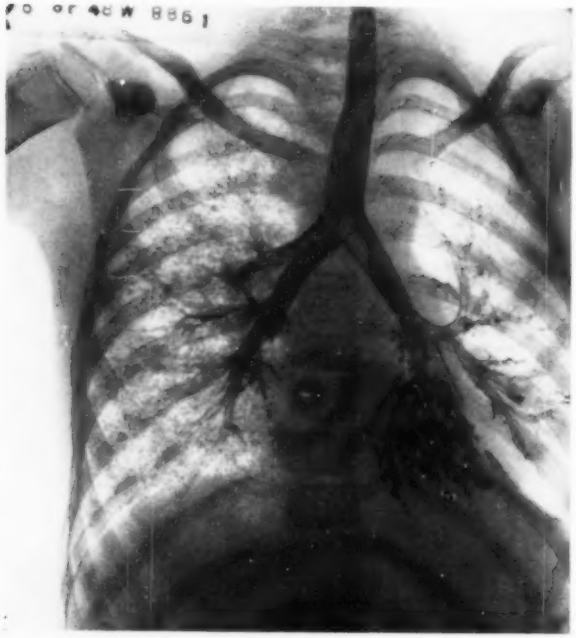


FIG. 190.—*Case* 14. Pre-operative film. Collapse and bronchiectasis of left lower lobe.

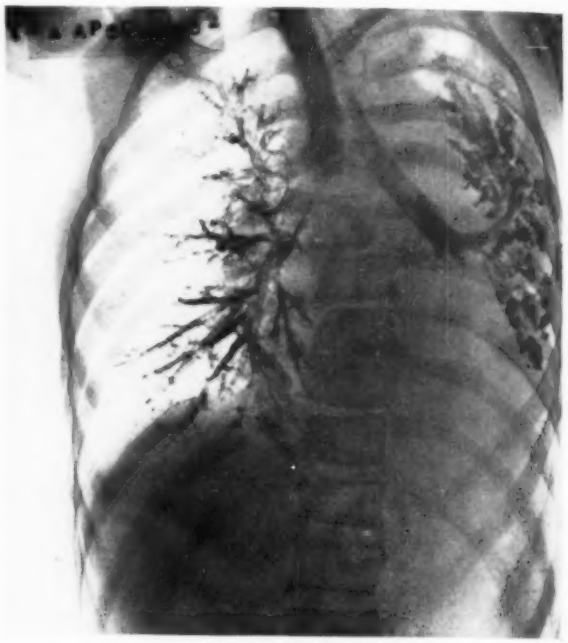


FIG. 191.—*Case* 14. Film 18 months after operation. Bronchiectasis in expanded left upper lobe.

FIG. 192.—*Case* 4. Pre-operative film. Bronchiectasis, anterior segment of right upper lobe.

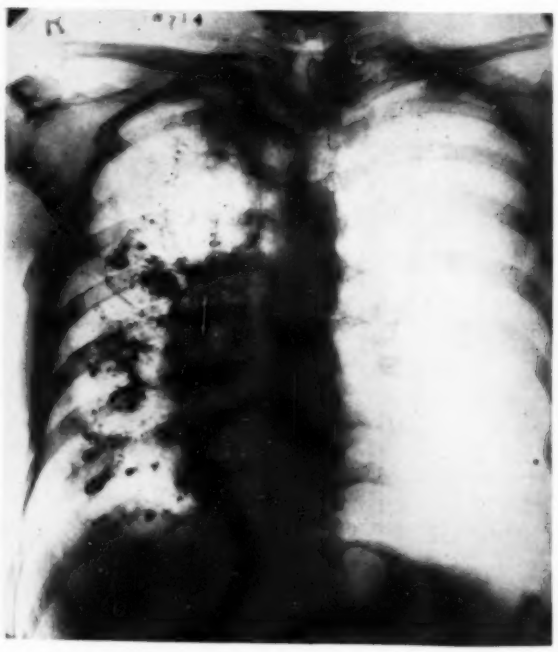


FIG. 193.—*Case* 4. Bronchiectasis developing after an acute necrotizing infection 3 years after resection of anterior segment of right upper lobe.

and particularly by the bronchoscopic observation of the persistence of chronic tracheobronchitis after suitable physiotherapy and antibiotic treatment.

It should be realized that not only the precision of the operation but the length of the operative time is a factor in the post-operative morbidity. The time factor not only indicates the difficulty of the operation, but this morbidity rate obtains in respect of the comparative results of a slow operator and a surgeon.

Either form of collapse demands vigorous physiotherapy, correct antibiotic treatment, and bronchoscopy, which must be repeated as often as necessary.

Table IV.—MORTALITY

Collapse		Chronic Infection	Acute Infection	Pleural Tuberculosis
Apneumatosis	Fibrosis			
Case 2, bronchopneumonia, refused further treatment	*Case* 1, acute abdomen *Case* 7, cor pulmonale 7 yr. later	None	*Cases* 3 and 4, acute tuberculosis 11 mth. and 2 yr. after further surgery	None
(1 case out of 4)	(2 cases out of 8)	(of 2 cases)	(2 cases out of 2)	(of 3 cases)

Total: 5 deaths in 19 recurrences

Table V.—RESULTS OF FURTHER SURGERY

Collapse cases		
Apneumatosis	3 cases all satisfactory	(*Cases* 8, 12, 17)
Fibrosis	2 dead, 6 satisfactory	(*Cases* 1, 7, 10, 13, 15, 16, 18, 19)
Chronic infection	1 satisfactory	(*Case* 14)
	1 small sinus	(*Case* 11)
Acute infection	2 dead	(*Cases* 3, 4)
Pleural tuberculosis	3 cases, 2 with sinus, but man is a clerk and woman does her housework	(*Cases* 5, 6, 9)

Total re-operated upon: 18; 4 dead, 10 satisfactory, 4 at light work, but each with a sinus.

Bronchoscopy should be done at once to prevent the peripheral migration of secretions and to obtain an accurate bacteriological examination of the aspirate.

In one case of collapse and recurrent effusion (*Case* 17), which did not respond to bronchoscopy, physiotherapy, antibiotics, and aspiration, decortication was done a month after resection, but this lobe had to be removed 16 months later.

Acute necrotizing infections must be treated in accordance with accepted principles, but stress must be placed on the treatment of the more chronic infection. This is of insidious onset, but can be diagnosed on X-ray screening by a clouding and relative lack of movement of the area. This demands the use of a broad-spectrum antibiotic, as no particular organism has been found to account for the lesion, and vigorous physiotherapy when the condition tends to clear up, which it will not do if the patient is left to rot in bed. It is important to screen all post-operative cases frequently for the first two years to make sure there is good movement and clear lung-fields.

Finally, it seems reasonable to give at least a fortnight's course of streptomycin in case a latent focus has been unwittingly disturbed at operation, in the hope that it will prevent a rekindling of a tuberculous infection.

RECURRENCE AFTER RESECTION IN BILATERAL DISEASE

There were 4 cases of recurrence in 24 resections in 15 patients. One died of secondary hæmorrhage a week after a second resection, the second has not been improved by further surgery, but the remaining two have benefited by further resection. These figures are too small for any conclusion to be drawn, but suggest the added risks of bilateral disease.

CONCLUSION

The operative mortality of unilateral subtotal resection was nil in this group of 203 consecutive cases.

The recurrence rate was 9 per cent and further surgery in recurrent cases gave a satisfactory result in over 50 per cent of cases, figures which should now be reduced to 5 or 6 per cent recurrence with 75 per cent good results by the application of the suggested measures.

Acknowledgements.—It is a pleasure to acknowledge my indebtedness to the senior lady almoner, Miss C. Farrar, and her staff for all the work involved in tracing these patients.

REFERENCES

CHESTERMAN, J. T. (1943), *Arch. Surg., Chicago*, **47**, 448.
— — (1951), *Brit. J. Surg.*, **39**, 263.
— — (1955 a), *Brit. J. Tuberc.*, **49**, 174.
— — (1955 b), *Ibid.*, **49**, 280.

THE USE OF CAVAL CATHETERIZATION IN CASES OF SEVERE OLIGURIA AND ANURIA

By J. W. CHAMBERS
SENIOR LECTURER IN CLINICAL BIOCHEMISTRY
AND GEORGE SMITH
SENIOR LECTURER IN SURGERY
FROM THE UNIVERSITY OF GLASGOW AND STOBHILL GENERAL HOSPITAL, GLASGOW

SEVERE oliguria or anuria is a not infrequent complication encountered in surgery and obstetrics. There are three main groups of aetiological conditions: (1) Circulatory renal insufficiency; (2) Parenchymatous renal damage; and (3) Obstruction to urine outflow. Only Groups 1 and 2 will be considered here.

Circulatory renal insufficiency is a common cause of oliguria resulting as it does from oligæmia of shock, hæmorrhage, and dehydration. The renal dysfunction is not due to organic kidney disease, and if treated promptly it can usually be corrected by replacing blood, fluids, and electrolytes as required; but if treatment is delayed it may lead to parenchymatous renal damage in the form of acute tubular necrosis. There is a further relationship between Groups 1 and 2. A patient with renal damage may become dehydrated owing to excessive vomiting or due to the damaged kidneys failing to conserve water and electrolytes, thereby adding circulatory renal insufficiency to already existing kidney disease.

The type of renal parenchymatous damage with which we are most concerned here is acute tubular necrosis. This lesion may result from prolonged hypotension due to hæmorrhage and shock, from transfusion of incompatible blood, from extensive burns, and from crushing types of injury. It may also be caused by chemical poisons such as mercuric chloride, carbon tetrachloride, and phenolic substances, or by bacterial toxins. Some cases appear to follow the administration of sulphonamides, particularly if the patient is dehydrated.

In obstetric practice, acute tubular necrosis is a recognized complication of abortion, particularly where sepsis is present, of criminally induced abortion, and of severe pregnancy toxæmia, especially if this latter is complicated by accidental hæmorrhage. In many instances, both hypotension and toxic factors coexist. Lastly, acute renal failure and circulatory renal insufficiency may be superadded to pre-existing chronic renal damage.

It is essential to look for cases of acute renal failure by prompt assessment of all cases of oliguria and to institute immediate adequate treatment. In most cases the prognosis is excellent. The aim is to keep the patient alive in as near a physiological state as possible until the damaged tubules slowly resume normal function.

Table 1.—DETAILS OF 10 PATIENTS UNDERGOING CAVAL CATHETERIZATION

CASE	SEX	AGE	ROUTE OF THERAPY		DAY OF DIURESIS	SERUM UREA		OUTCOME
			Gastric	Caval		Highest Level	Final Level	
		(years)	(days)	(days)		(mg. per cent)	(mg. per cent)	
1	F.	26	1	16	17	264	26	Recovery
2	F.	43	2	15	10	320	24	Recovery
3	F.	34	23	25	22	480	108	Death
4	F.	43	2	19	—	536	536	Death
5	F.	48	4	11	9	280	33	Recovery
6	M.	60	3	9	13	256	188	Death
7	F.	40	3	7	—	536	536	Death
8	M.	49	—	4	6	268	25	Recovery
9	F.	47	—	8	—	51	25	Recovery
10	F.	30	—	9	—	34	29	Recovery

In the period 1950–7, 29 cases of acute renal failure have been treated in the Glasgow Northern Group of hospitals (Sectoral Hospital, Stobhill General Hospital). This group has more than 3000 beds, of which about 550 are in Obstetrics and Gynæcology. Broadly, the categories of cases treated were: obstetric, 13; medical, 6; pædiatric, 6; and surgical, 4. Of these 29 cases, there have been 4 deaths.

All of these cases were treated according to the principles and practice recommended by Bull, Joekes, and Lowe (1949) and Evans, Jones, Milne, and Yellowless (1953). The essential feature of the therapy is to restrict basal daily intake to about 700 ml. of a 50 per cent solution of glucose in water. This is usually given through an indwelling stomach tube of the Ryle type. If, however, there is excessive vomiting, or if diarrhœa or intestinal ileus occurs, the intragastric route is replaced by caval infusion. Peripheral veins cannot be used for the continued infusion of this grossly hypertonic fluid. Of the 29 cases, 8 required the caval route. In addition to these acute renal failure cases, 2 gynæcological patients with severe post-operative illness and intestinal obstruction required prolonged intravenous therapy. Since suitable peripheral veins had been used up, caval catheterization was resorted to. These 10 severely ill patients are described in this paper (*Table I*). A more detailed account of these and

the other cases is to be presented elsewhere (Barr and Chambers, 1957).

METHOD

A No. 9F. nylon catheter of the type used for cardiac catheterization is inserted into the right femoral vein via a cut-down on the upper end of the saphena magna vein. The catheter is advanced into the inferior vena cava and positioned so that the tip lies above the renal veins in the region of the hepatic venous inflow (*Fig.* 194). This can be done with the patient in bed and the catheter position verified, and adjusted, if need be, by reference to radiographs made on a portable machine. By this means, the venous return from the major part of the body is available to dilute the hypertonic glucose solution immediately it leaves the catheter tip. When the superior vena cava is used, dilution of the solution by the blood is not so great. We have used this route in one instance (*Case* 10), where there was frank pelvic peritonitis. The catheter was placed so that the tip lay 1 in. from the point of entry of the superior cava into the right atrium.

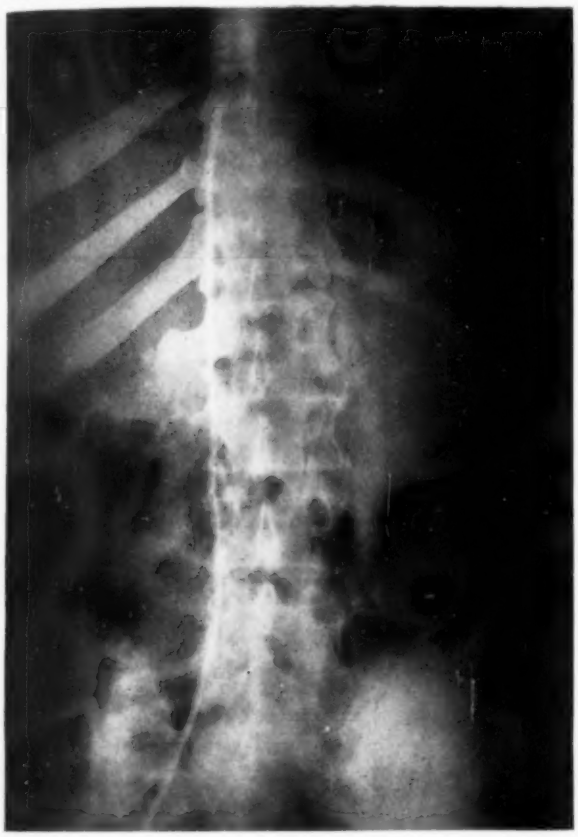


FIG. 194.—Radiograph showing catheter in position in inferior vena cava.

After placement of the catheter, the cut-down wound is closed around the catheter and an occlusive dressing applied. The excess catheter protruding from the wound is then strapped to the limb, allowing the patient to move freely about in bed (*Fig.* 195). The comfort of the patient is noteworthy when compared with one who is having multiple peripheral venous infusions.

There has been no significant clotting in the veins even with the catheter in place and carrying 50 per cent glucose for many days. The longest period was in *Case* 3, where the catheter was in place for 25 days, although in this case the fluids used were much less hypertonic. It is of the greatest importance that, for the duration, fluid must be kept flowing through the catheter lumen. To this end, a Y-piece is connected to the tubing attached to the catheter. This allows fluid from a second reservoir to flow into the cava while the first reservoir is being changed. If at any time blood is allowed to reflux into the catheter, either by stopping the forward flow or by pinching the attached tubing, contact with hypertonic glucose may lead to clotting in the narrow bore of the catheter. With care this can be avoided.

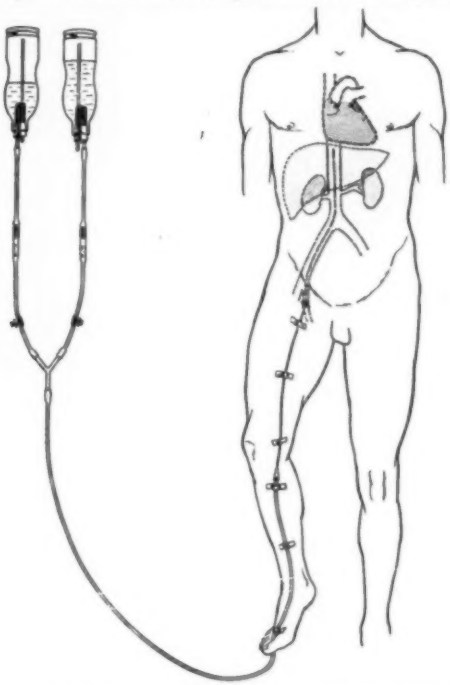


FIG. 195.—Schematic drawing showing catheter inserted via upper end of saphena magna vein.

Heparin is added in a dose of 1000 international units per 500 ml. of fluid. In spite of this, compact white thrombus tends to form around the outside of the catheter near the tip and there is a tendency for clot to form where the catheter is in contact with the vein wall (*see Fig.* 199). In spite of these conditions revealed at autopsy, there has been no clinical evidence of complications such as pulmonary embolism, or any trouble on withdrawing the catheter at the cessation of treatment. There has been no wound sepsis at the point of catheter insertion.

CASE REPORTS

Case 1.—Female, aged 26 years, admitted with spontaneous abortion at 6 months. The signs and symptoms were comparable to those of accidental hæmorrhage. The progress and biochemical results are shown in *Fig.* 196. This patient passed less than 50 ml. of urine per day for 9 days. She had jaundice with a serum bilirubin level of 10·0 mg. per cent at the onset of the renal failure. Other complications in chronological order were persistent vomiting (blood-stained), herpes labialis,

ulceration of tongue and pharynx, acute pericarditis, uræmic twitchings, irritability, drowsiness, slight nerve deafness, cystitis, potassium depletion, thrombophlebitis of arm veins, and prolonged tachycardia. The caval œdema and cardiac insufficiency, and finally jaundice before death.

At autopsy there were healed pyæmic abscesses in the viscera. The primary focus of infection appeared

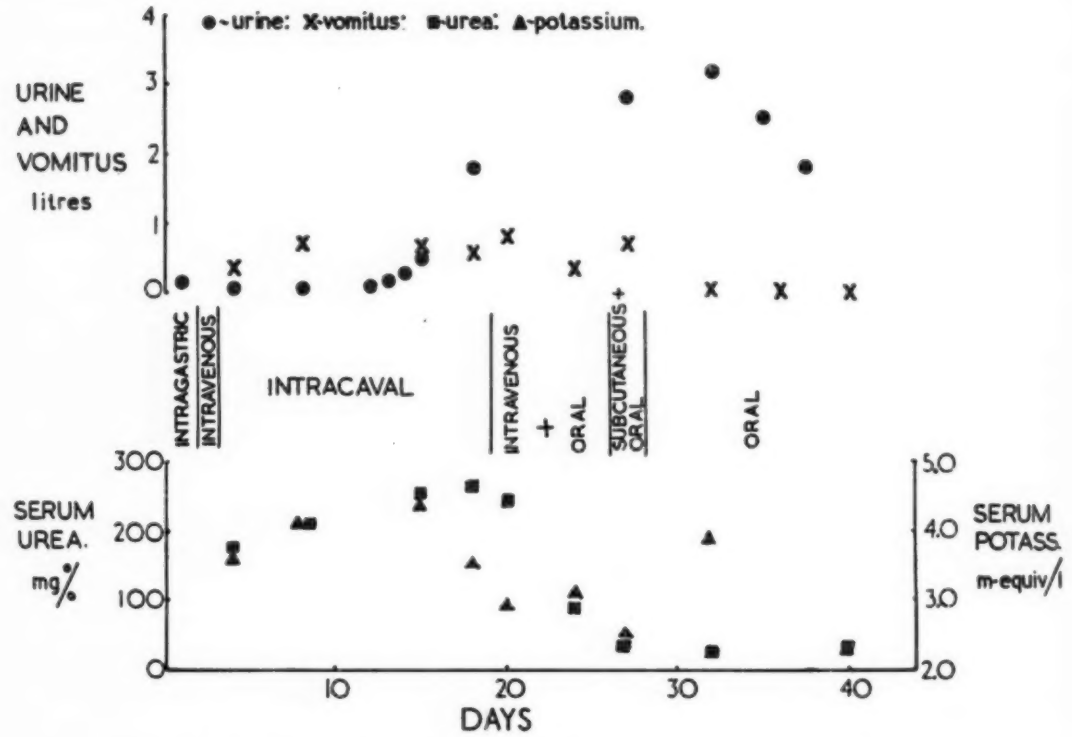


FIG. 196.—*Case* 1. Female, aged 26 years. Progress and biochemical results.

catheter was in place for 16 days. She made an excellent recovery with normal renal and liver function tests. Two and a half years later, the patient has just had a normal pregnancy and delivery. At present the blood-pressure is normal, as are all serum biochemistry analyses and the urea clearance. There is no proteinuria. The caval catheter had been inserted via the right femoral vein. There is no swelling of that leg and the calf circumference is the same as that of the left calf.

Case 2.—Female, aged 43 years, admitted with anæmia and low blood-pressure following abortion at 5 months. Two pints of whole blood and two pints of plasma were required to raise the blood-pressure to within normal limits. The caval catheter was in situ for 15 days. The blood-urea level was normal 18 days after the onset of diuresis. The left leg was a little swollen at time of dismissal.

Case 3.—Female, aged 34 years, para 6, admitted with profuse post-partum hæmorrhage following a stillbirth at home (7½ months). She was shocked; hæmoglobin level was 4 g. per cent, and the initial serum urea level was 270 mg. per cent. Two pints of whole blood and the packed cells from 5 pints were transfused. There was marked diarrhœa and evidence of pericarditis. Later the patient became semi-comatose and showed twitching. She improved as the diuresis increased to 2 litres a day. Thereafter, staphylococcal septicæmia developed, then to be in the pelvis. There was liver necrosis and renal tubular necrosis, both showing some healing. In the inferior cava there was a firm adherent tubular

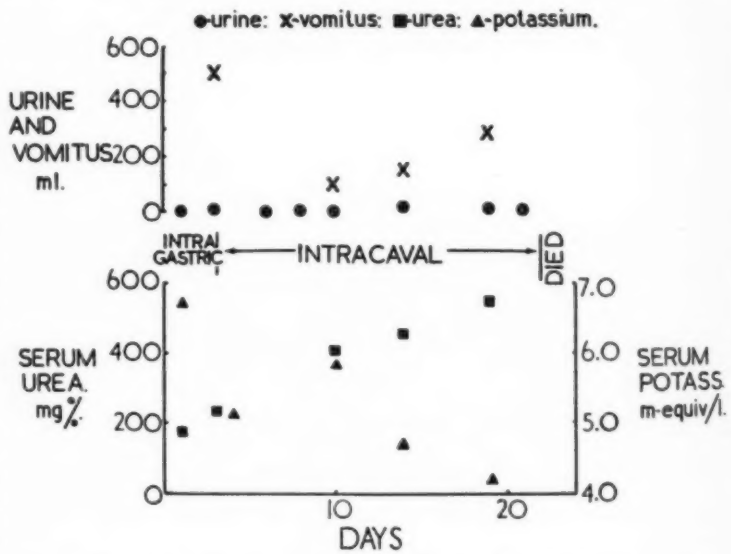
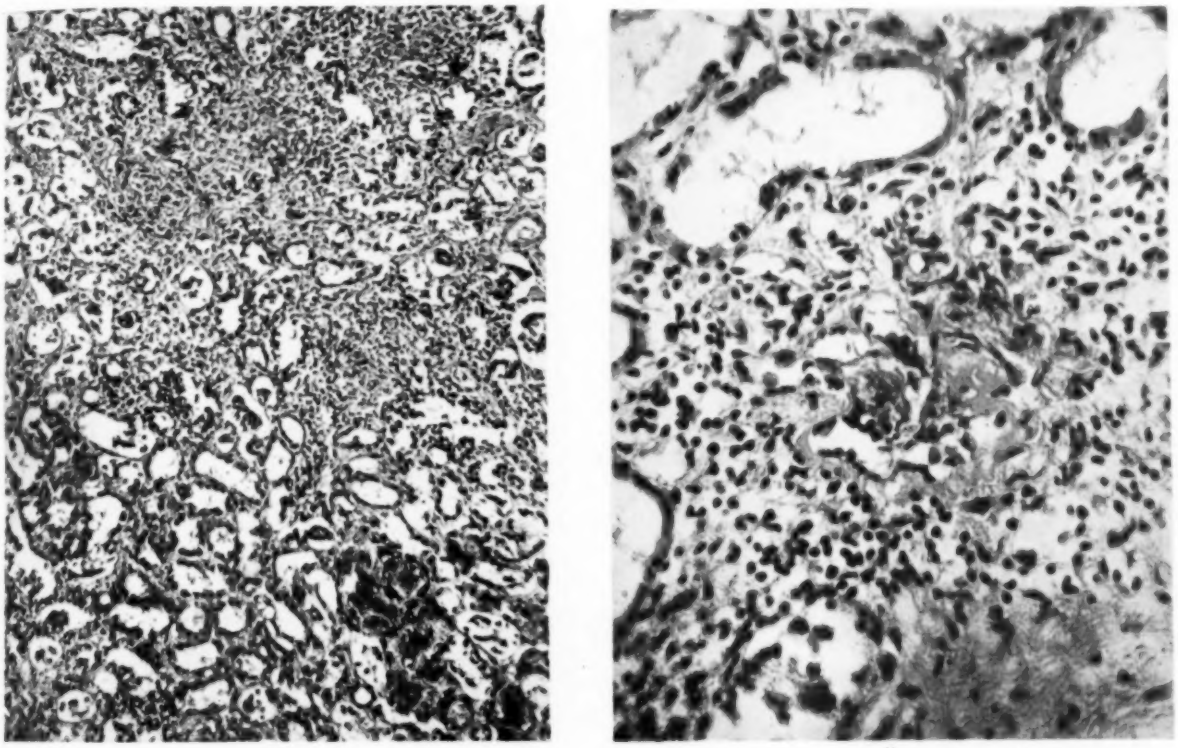


FIG. 197.—*Case* 4. Female, aged 43 years. Progress and biochemical results.

fibrinous cast of the cardiac catheter, but no damage to the vein wall. The catheter had been in place for 25 days.

Case 4.—Female, aged 43 years. Oliguria was noted in the dermatology ward, to which the patient had been admitted with a skin rash which was provisionally diagnosed as due to aspirin sensitivity. Throughout the period of caval treatment, hydration and blood-pressure were satisfactory. The course and biochemical results are shown in *Fig.* 197. The total urinary output in 22 days was 225 ml. (8 fl. oz.). The patient remained in



A B

FIG. 198.—*Case* 4. A, Renal cortex showing remains of several glomeruli and some disintegration of the tubules. H. and E. (× 100.) B, Destroyed glomerulus with remnants of capillary loops and a small portion of hyalinized capsule on the right. H. and E. (× 300.)

A B

FIG. 199.—*Case* 4. A, Autopsy specimen showing patches of mural thrombus on inferior vena cava endothelium (catheter in place for 19 days). B, Close-up of one of the mural thrombi on the inferior vena cava, showing firm adherence to endothelium.

good condition until 3 days before death. Vomiting was not prominent.

At autopsy the kidneys showed almost complete destruction of all glomeruli (*Fig.* 198). A full description of the pathology of this case has been published by Dick (1957). The inferior vena cava showed little damage to the endothelium; only a few small adherent thrombi were present (*Fig.* 199), although the catheter had been in place for 19 days.

Case 5.—Female, aged 48 years. Oliguria was noted after the patient had been admitted to a fever hospital with pyrexia of unknown origin and a generalized rash. She had been on a course of sulphonamide 10 days before this. The initial serum urea level was 200 mg. per cent. Vomiting and diarrhœa made the caval route necessary. On this, the serum urea reached normal levels in 14 days, but rose again to 68 mg. per cent on increasing the food protein intake. From one month later the serum urea has remained at normal levels. There has been no swelling of the legs.

Case 6.—Male, aged 60 years, admitted with a rupture of a dumb-bell shaped atherosclerotic aneurysm of the lower aorta and left common iliac artery. This was dealt with successfully. Some 5 pints of blood and clot were removed from the retroperitoneal area and 7 pints had to be transfused rapidly before the patient was fit for operation. This period of marked hypotension precipitated renal damage. A diuresis was obtained after 9 days of caval therapy, and the catheter was withdrawn after 11 days. The patient died suddenly 17 days after operation. On that day the serum urea had come down to 188 mg. per cent. No autopsy was carried out.

Case 7.—Female, aged 40 years, very obese with extensive uterine cervical carcinoma invading the bladder. The growth had previously been treated unsuccessfully with radium. There was severe pain. Removal of the uterus and bladder was carried out with transplantation of the ureters into the colon. The site of operation was grossly matted with adhesions, but the tumour was widely excised. There was one episode of coma and collapse on the fourth post-operative day. The patient's general condition then improved, but there was complete anuria for 6 days. During this time caval therapy was instituted. Later a few ounces of urine were passed per vaginam and a fæcal fistula occurred. The patient died 12 days after operation. No autopsy was carried out.

Case 8.—Male, aged 49 years, operated on for biliary colic. A cholecystectomy was performed. There was post-operative collapse with the development of auricular fibrillation. Oliguria persisted for 5 days. The patient could not tolerate oral glucose or gastric intubation. After 4 days of caval therapy a satisfactory diuresis occurred, and his treatment was carried on with oral therapy supplemented by the intravenous route.

Case 9.—Female, aged 47 years, admitted with intractable abdominal pain due to endometriosis. She underwent operation for removal of uterus, tubes, and ovaries. There was post-operative deterioration with marked vomiting. A large pelvic hæmatoma formed which became infected and pelvic peritonitis accompanied by intestinal obstruction developed. A laparotomy followed which partially relieved the obstruction. Vomiting, however, continued, and caval therapy was instituted via the right femoral vein. The patient developed fever and a blood-culture was positive for staphylococcus. This was readily controlled by antibiotic treatment. Still later the patient developed deep vein thrombosis in the right leg. This was treated by phenylindanedione.

When seen 7 months after dismissal from hospital, the patient, otherwise well, showed an increase of 1 in. in the circumference of the right leg at mid-calf level. Swelling, however, is normally controlled by wearing an elastic stocking.

Case 10.—Female, aged 30 years, admitted with puerperal peritonitis. Intestinal ileus with copious vomiting was present. The aspiration loss eventually reached about 3 litres per day. Intravenous infusions sufficed to keep the serum urea and electrolytes within normal limits. Mechanical obstruction due to pelvic abscess and bowel adhesions necessitated laparotomy followed by a second intervention later. Before this, available superficial veins had been exhausted and a caval drip was set up, the catheter being passed through the left median basilic vein into the superior vena cava. This route was chosen in view of the known pelvic peritonitis. The caval drip was run for 8 days when the patient was able to take over on oral therapy. When seen 6 months later the patient was well and there was no evidence of damage to the venous drainage of the left upper limb.

CONCLUSIONS

We are in no doubt that the 6 patients who survived to regain full health owe their lives to this procedure of intracaval therapy. Two of the four deaths were in no way related to the therapy (*Cases* 3 and 4). In the absence of post-mortem examination in *Cases* 6 and 7, it is not possible to eliminate the caval drip from blame. It can only be stressed that there was no evidence that it had in any way contributed to the fatal outcome. Indeed, when one considers that these two cases represent on the one hand an emergency operation for a ruptured aorticoiliac aneurysm, and on the other, pelvic exenteration for uterine carcinoma, the fact that death was delayed for 17 and 12 days respectively after operation, suggests that the prolongation of life may have depended on the prompt institution of caval therapy.

Lastly, although there have been no signs of pulmonary emboli, in 2 cases (*Cases* 2 and 9), there is residual evidence of deep vein thrombosis. In *Case* 9 this is on the same side as the catheter insertion; in *Case* 2 it is on the opposite side.

We believe that none of the fatal cases could have been saved by artificial kidney treatment.

Acknowledgements.—We wish to express our thanks to the medical and nursing staff of the Glasgow Northern Hospital Group for their assistance with therapy.

We are indebted to Dr. J. C. Dick for supplying Figs. 198 and 199, and to the Editor of the *Journal of Clinical Pathology* for permission to publish these figures.

REFERENCES

BARR, J. S., and CHAMBERS, J. W. (1957), *Scot. med. J.*, in the press.

BULL, G. M., JOEKES, A. M., and LOWE, K. G. (1949), *Lancet*, **2**, 229.

DICK, J. C. (1957), *J. clin. Path.*, **10**, 168.

EVANS, B. M., JONES, N. C. H., MILNE, M. D., and YELLOWLEES, H. (1953), *Lancet*, **2**, 791.

MULTIPLE MALIGNANT PRIMARY NEOPLASMS

By ANTONY F. WALLACE

SURGICAL REGISTRAR, AND LATE CANCER REGISTRAR, UNIVERSITY COLLEGE HOSPITAL, LONDON

A PATIENT with a malignant neoplasm has a right to know whether cure is possible and whether another growth will develop later on. The question cannot at present be answered, as factors governing the incidence and spread of malignant disease in human beings are largely unknown. A positive answer may come from the presence of a strong family history, from a history of exposure to carcinogens, from knowledge of those diseases associated with a high incidence of malignant disease, and from statistical studies.

At University College Hospital, London, all patients with malignant disease are followed up from the date when their treatment began or, if not treated, from the date when they were first seen. If a patient who was first treated at another hospital is followed up, his records date from the time at which his treatment began at that hospital. One per cent of patients only remain untraced and their follow-up incomplete. Between January, 1946 and December, 1950, 3006 patients with malignant disease were seen. (The terms neoplasm and tumour have been used synonymously in describing primary disease in these patients.) Included in this total are all brain, pituitary, and spinal-cord tumours, whether histologically benign or malignant. Papillomata and carcinomata of the bladder are taken together in one group. Data on 134 patients in this group who developed more than one primary neoplasm are included in this paper. The author has attempted to present interesting facts in an interesting way. Some conclusions are drawn, none of which is based on statistical analysis.

Billroth in 1879 proposed certain conditions which had to be satisfied before a diagnosis of multiple primary tumours could be established :—

1. Each tumour must have an independent histological appearance.
2. The tumours must arise in different situations.
3. Each tumour must produce its own metastases.

These stringent criteria can best be applied to autopsy material. In this clinical study three different rules have been used for each patient :—

1. Macroscopically and microscopically each tumour must be *distinct*.
2. Each tumour must grow in an individual way.
3. The diagnosis may be confirmed by the different character of the metastases in each case.

Special conditions obtain with certain growths.

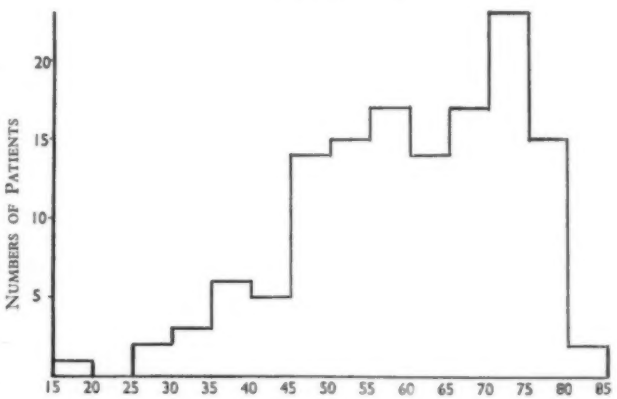
1. Papillomata and carcinomata of the urinary bladder may be single, multiple, recurrent after treatment, or metastatic by implantation. For this reason all bladders containing neoplasms are counted once only and no attempt has been made to identify multiple tumours.

2. Both ovaries may develop a primary tumour. When seen at operation and at autopsy a mass of malignant ovarian tissue frequently involves both ovaries. It is impossible to obtain a consecutive series purporting to show patients with ovarian tumours as having a single primary neoplasm, or multiple primary neoplasms, either with or without ovarian metastatic deposits. Therefore no attempt has been made to record primary carcinoma of the ovary as arising in one or both organs. (Certain values given later are therefore too small.)

PATIENTS DEVELOPING MULTIPLE PRIMARY TUMOURS

Between January, 1946 and December, 1950, 3006 patients having 3096 primary neoplasms attended : 71 developed two primary tumours between 1946 and 1950 ; 35 developed one tumour between 1946 and 1950 and had another primary tumour within five years before or after the first.

Table I.—AGE OF 134 PATIENTS AT TREATMENT FOR FIRST NEOPLASM



AGES (in 5-year groups, i.e., 15–19, 20–24, etc.)

Of these 106 patients 13 developed three or more primary tumours between 1946 and 1950 ; 2 others had had one or more tumours before the earliest one in the 1946–50 period (i.e., three or more primary tumours in all). Four others had one or more tumours later than five years after the first in the 1946–50 period (i.e., three or more primary tumours in all).

In these 106 patients 240 primary neoplasms occurred. Twenty-eight *additional* patients developed one primary neoplasm in the 1946–50 period and a second more than five years before or after it (recorded up to December, 1954). Three of these patients developed three primary tumours in all ; 59 primary neoplasms occurred in these 28 patients.

Altogether, 112 patients each developed 2 primary neoplasms ; 16 developed 3 ; 3 developed 4, and 3 developed 5 primary neoplasms.

A total of 299 primary neoplasms, excluding multiple bladder and ovarian tumours, occurred in 134 out of 3006 patients considered (i.e., 4·5 per cent

of patients developed two or more primary neoplasms); 55 per cent (74) of these patients were male and 45 per cent (60) were female. The age of these patients at attendance for treatment of a first neoplasm is given in *Table I*. Forty patients developed all their primary malignant tumours after the age of 70.

SITES IN WHICH MULTIPLE PRIMARY TUMOURS DEVELOP

Table II shows firstly the distribution of multiple tumours in their different tissues of origin. It is not intended that one should compare their numbers (as percentages) with the percentage distribution of all the 3096 neoplasms from which they have been selected. No allowance or correction has been made for the length of time different patients survive after treatment of their first neoplasm. Many are still alive. This 'survival' factor may partially explain why multiple primary tumours are found often in some organs but rarely in others. A second neoplasm will usually have time to show itself only when the first grows slowly, or it is successfully treated.

Generalized changes occur in the skin, the mouth, the ovaries, the breasts, the liver, the large bowel, and the urinary bladder, which predispose to the development of multiple carcinomata in these organs. In *Table II* 60 patients are shown to have had two or more primary tumours in one organ or tissue. In all but two of these patients the tumours occurred in organs commonly associated with multiple primary neoplasms. The expectation of life of patients with carcinomata of the bronchus and sarcomata is short, and therefore the fact that an example of a double primary tumour is rare in a lung and in connective tissue does not detract from its possible significance. (*Cases* 1 and 2 are examples.)

Table III shows that of the three patients in this series who suffered from an intrinsic carcinoma of the larynx, two subsequently died from a primary carcinoma of the bronchus. These two men (*Cases* 3 and 4) could be considered with *Case* 1 as possible examples of patients having a generalized precancerous change throughout their respiratory tract, or as cases in which malignant cells might have travelled down the trachea and become implanted in the bronchial mucosa. From the table it can be seen that both of the men in this series who developed a carcinoma of the prostate gland also developed a bladder tumour. It was a carcinoma of the bladder in each case. No significance can be attached to this combination of tumours in only 2 patients.

Table II.—Distribution of Multiple Tumours in Different Tissues of Origin

	299 Tumours arising in 134 Patients		60 Patients having Multiple Tumours arising in One Tissue	Percentage of Tumours occurring in each Tissue in the Total 3096 Tumours
	Number of Tumours	Percentage of Tumours		
Skin (including melanoma)	116	38	40*	10
Breast	39	13	6	22
Colon, rectum, anus	31	10	7	8
Mouth (lips to hypopharynx)	23	8	5†	7
Bronchus	16	6	1*	11
Bladder (papilloma, carcinoma)	13	4	(Not analysed)	4
Stomach	10	3	0	6
Brain (benign and malignant)	7			
Corpus uteri	7			
Ovary	6		(Not analysed)	
Cervix uteri	5			
Reticulo-endothelial system	5			
Sarcoma (all sites)	4		1	2
Larynx	3			The percentage is less than 5 for these other tissues
Pancreas	2			
Prostate	2			
Kidney (hypernephroma)	1			
Melanoma (excluding skin)	1			
Œsophagus	1			
Pituitary	1			
Spinal Cord	1			
Testis	1			
Trachea	1			
Vulva	1			
Carcinomatosis	2			

* *Case* 1 is counted under 'skin' and 'bronchus'. † *Case* 5 is not included.

CASE REPORTS

Case 1.—Mr. S. E., a clerk, attended this hospital in September, 1950, complaining of aching in his ankles, knees, elbows, and wrists since June, 1950. He was 48 years old. An epithelioma of the skin of his left shoulder had been treated at another hospital by radiotherapy in 1948. An epithelioma of the skin over the outer side of his right ankle had again been treated by radiotherapy at the same hospital in February, 1949.

On examination here he had hypertrophic pulmonary osteo-arthropathy and a chest radiograph showed a lesion in the left upper zone. He was bronchoscoped and no abnormality was seen. At thoracotomy on Sept. 19, 1950, there was a peripheral mass in the posterior basic segment of the left lower lobe and the upper lobe anteriorly was firmly adherent to the chest wall, held there by a separate mass of growth. A palliative pneumonectomy was performed.

The lung contained these two tumour masses only. Histological examination revealed an anaplastic squamous-cell carcinoma in the upper lobe and an adenocarcinoma in the lower lobe. The hilar glands contained metastatic carcinoma. Each was considered to be a primary carcinoma of the bronchus.

His chest was treated by radiotherapy in December, 1951, when recurrent growth caused severe pain. He developed a pleural effusion and died in May, 1952. No autopsy was performed.

Case 2.—Mr. A. L., a publisher's assistant, had a tumour excised from the upper part of his right thigh in August, 1948, at another hospital. He was aged 66 and had first noticed the lump three months previously. Histological examination showed an active pleomorphic sarcoma too anaplastic to allow its tissue of origin to be determined. He was referred here and a course of radiotherapy to his right groin, which included the operation area, was begun in November, 1948.

In December, 1952, he noticed a lump over the inner side of his right knee in quite a different place from his earlier sarcoma. This was excised with ¼ in. margin of apparently normal skin around it in January, 1953. Histological examination showed a myxosarcoma of low-grade malignancy. There was no similarity between this tissue and his previous active sarcoma. This myxosarcoma recurred locally and was excised again in May. It recurred a second time and was excised in September, 1951, together with the deep fascia beneath it and a 1½ in. margin of apparently normal skin around it. Both recurrences were sectioned and the diagnosis confirmed.

When he was last examined in April, 1956, there was no evidence of local recurrence or spread of either of his sarcomata.

Case 3.—Mr. A. B. attended in March, 1947, complaining of a husky voice for eight months. He was aged 66 and worked as a sweeper in a saw-mill. In the same month his left vocal cord was excised and histological examination confirmed the diagnosis of an early carcinoma with submucous infiltration.

In March, 1949, he began to lose weight and in November he developed a cough with blood-stained sputum. A chest radiograph taken in December showed a left hilar opacity. In April, 1950, a firm radiological diagnosis of a primary carcinoma of the bronchus was made. Bronchoscopy at that time showed no evidence of local recurrence in the larynx, the left main bronchus

Table III.—Number of Times Patients with One or More Primary Neoplasms in One Tissue Developed a Primary Neoplasm in any other Tissue

	Skin (including melanoma)	Breast	Colon, rectum, anus	Mouth (lips to hypopharynx)	Bronchus	Bladder (papilloma, carcinoma)	Stomach	Brain (benign and malignant)	Corpus uteri	Ovary	Cervix uteri	Reticulo-endothelial system	Sarcoma (all sites)	Larynx	Pancreas	Prostate	Kidney (hypernephroma)	Melanoma (excluding skin)	Œsophagus	Pituitary	Spinal cord	Testis	Trachea	Vulva
Skin (including melanoma)	40																						
Breast	6	6																					
Colon, rectum, anus	5	3	7																				
Mouth (lips to hypopharynx)	4	1	2	5																			
Bronchus	5	2	1	1	1																		
Bladder (papilloma, carcinoma)	1	2	1	1	1	?																	
Stomach	2	1	1	2		1																	
Brain (benign and malignant)		1	1		1	1	1																
Corpus uteri	1	2		1	1	1																	
Ovary	1	3	1						1	?													
Cervix uteri		3						1		1													
Reticulo-endothelial system		1		1		1	1		1														
Sarcoma (all sites)				1									1										
Larynx			1		2																		
Pancreas	1	1																					
Prostate						2																	
Kidney (hypernephroma)						1																	
Melanoma (excluding skin)							1																
Œsophagus	1																						
Pituitary								1															
Spinal Cord													1										
Testis	1																						
Trachea		1																					
Vulva			1																				

The skin is the most frequent site of tumour formation, the vulva one of the least. The other sites are listed in order between these two extremes. (*See Table II.*)

was full of pus, but no growth was seen. Sputa contained no tubercle bacilli. His pulmonary lesion was visible at a very early stage on a radiograph taken in January, 1948.

By September, 1950, his left lung had collapsed completely.

He was last examined at this hospital in April, 1951, when there was no evidence of local recurrence of his carcinoma of the larynx, but his respiratory symptoms were severe. He died from his carcinoma of the bronchus in August, 1951, 43 months after its first appearance. No autopsy was performed.

Case 4.—Mr. A. C., a music-hall artist aged 62, attended in June, 1948, complaining of a hoarse voice for one year. His thickened right vocal cord was biopsied, was performed. Histological examination revealed a low-grade fibrosarcoma.

In January, 1952, he became ill and began to cough up blood and died in October with (? secondary) growth in his chest. It is possible that he died from a primary bronchial carcinoma. At no time was there evidence of local recurrence of his carcinoma or sarcoma of the tongue. No autopsy was performed.

CARCINOMA OF THE BREASTS, UTERUS, AND OVARY

Table III suggests that there may be an increased incidence of carcinoma of the uterus and ovary in patients developing a carcinoma of the breast.

Table IV.—Women with Two Carcinomata of Breasts, Uterus, and Ovary

Site of Tumour	Under 50		Over 50	
	Age in years when first tumour presented	Number of years before second tumour presented	Age in years when first tumour presented	Number of years before second tumour presented
Carcinomata of both breasts	37 39 47 49	1 1 1 1	54 73	24 1
Carcinomata of breast and corpus uteri			60 69	14 1
Carcinomata of breast and cervix uteri	44	3	60 70	3 7
Carcinomata of ovary and corpus uteri	46	1		
Carcinomata of ovary and cervix uteri	50	3		

section showed a squamous-cell carcinoma (Broder's Grade II), and a course of radiotherapy was given.

He became ill in January, 1951, and a radiograph taken at that time showed a left pleural effusion and a mass at the hilum of the left lung. In February, in addition to the physical signs in his chest and an increase in size of the hilar opacity seen on new radiographs, numerous skin deposits appeared. One was excised and showed secondary oat-cell carcinoma of bronchial origin.

He died in April, 1954, and at autopsy a carcinoma of his left main bronchus was found. There was no evidence of recurrence of his carcinoma of the larynx.

This series includes only one recognized example (*Case* 5) of a patient whose second malignant neoplasm probably resulted from the treatment of his first. This most interesting case was published by Deller in 1951 when the patient was still alive and free from evidence of the metastases from which he subsequently died.

Case 5.—Mr. C. M., a crane operator aged 48, attended with a typical carcinomatous ulcer underneath the right side of the anterior third of his tongue which he had noticed one month previously. This was treated with interstitial radium in October, 1929. The ulcer was not biopsied. The contents of his right submandibular triangle were removed surgically and a block dissection of the left side of his neck was performed in the next twelve months. No involvement of glands was demonstrated histologically.

In September, 1948, he noticed a lump in the left side of the middle third of the tongue. On examination, there was a whitish area of mucosa overlying a lump about ¾ in. in diameter which extended backwards from beneath the edge of the soundly healed scar remaining from his old carcinomatous ulcer. In October a left hemiglossectomy

However, a patient with carcinoma of the breast seems to be no more likely than anyone else with a neoplasm to develop a second primary tumour of the opposite breast. Care has been taken to avoid the error of misdiagnosing a metastasis as a second primary neoplasm in patients who develop a carcinoma in one breast, subsequent to a primary carcinoma of the other. Six women developed a primary carcinoma of each breast. When there was any doubt the case was excluded; therefore it is possible that multiple primary tumours of the breasts are in fact more common than appears from this series. (The figures given by Stalker, Phillips, and Pemberton (1939) support this suggestion—*see* Discussion.) Each of the 12 breast carcinomata occurring in the 6 women was excised at operation and submitted to histological examination, and each was identified as a primary tumour.

Data on women, each with two carcinomata of their breasts, uterus, and ovary, are presented in *Table IV*. All of the women with bilateral mammary carcinomata have lived at least five years after their second neoplasm presented. (A woman developing a metastasis in her breast would probably die before five years had elapsed.) Of the 13 women whose first tumour presented at or before they reached 50 years of age, all had their second neoplasm within three years of the first. Beyond 50 years of age the time interval between the two neoplasms is often longer.

DISCUSSION

The study of multiple malignant primary neoplasms (*Table V*) was for many years the province of

pathologists and the published series of autopsy data came from continental centres. Major, at Johns Hopkins Hospital, reviewed the subject in 1918, but it was not until the Mayo Clinic series of 1933 (Hurt and Broders) that live patients were primarily considered. Warren and Gates (1932) had presented a series of autopsy figures from Harvard University in the previous year and had studied the subject in detail.

Multiple malignant primary tumours were discussed by surgeons at the Royal Society of Medicine in London in 1930 (Norbury) and again in 1944 (Whigham), but no new series was presented. A brief tabular review appeared in 1950 (Williamson). Apart from these three publications the author has found no other papers written in this country. No reference is made to innumerable individual case reports which had been published in all parts of the world during this and the last century.

Shortly before the second world war Eisenstaedt (1938) reintroduced the subject into American medical literature, and Stalker and others (1939) discussed 2500 patients with malignant tumours seen at one centre in Minnesota. These figures are somewhat similar to those in this series and roughly comparable, although 55 per cent of their 113 patients with multiple malignant neoplasms were females; 4·5 per cent of their patients had multiple malignant tumours. About 40 per cent of patients developed all their tumours after the age of 70 years. The numerical distribution between the different tumour sites is again similar. For example, 35 patients each had more than one skin tumour, 38 neoplasms occurred in the colon, rectum, and anus, and 43 carcinomata of the breast are included. Thirteen patients are reported as having bilateral mammary carcinomata and this does suggest again that the figure given in the author's series is unusually small.

Table V.—FIGURES FOR MULTIPLE MALIGNANT PRIMARY NEOPLASMS FROM VARIOUS CENTRES

DATE	PLACE	TOTAL MALIGNANT TUMOURS	MULTIPLE PRIMARY MALIGNANT TUMOURS	PERCENTAGE OF MULTIPLE PRIMARY MALIGNANT TUMOURS	AUTHOR
	Italy	1154 autopsies	7	0·6	Bilello, Montanini
1914	Basel	966 autopsies	20	2·1	Egli
1916	Christiania (Norway)	4219 autopsies	32	0·8	Gade
1916	Oslo	524 autopsies	16	3·2	Harbitz
1926	Budapest	1559 autopsies	5	0·3	Puhr
1931	Leningrad	1238 autopsies	23	1·8	Gloriainowa, Schabad
1931	Mayo Clinic	950 autopsies	18	0·2	Hanlon
1932	Harvard University	1078 autopsies	40	3·7	Warren, Gates
1933	Mayo Clinic	2124 patients	71	3·3	Hurt, Broders
1934	Buffalo Institution, N.Y.	11,212 autopsies	307	2·7	Schreiner, Wehr
1934	Michigan University	983 autopsies	30	3·1	Bugher
1936	Wisconsin University	583 autopsies	46	7·8	Burke
1939	Minnesota University	2500 patients	327	13·1	Stalker, Phillips, Pemberto
1957	London, University College Hospital	3096 patients	299	9·7	Wallace

SUMMARY

Of 20 patients who attend hospital with a malignant tumour, one will develop later another primary malignant tumour. Patients should be examined at regular intervals to exclude recurrence and spread of their initial neoplasm, and to search for others at their earliest stage. In certain patients it may prove possible to predict the likely site of development of their next neoplasm.

Acknowledgements.—I would like to thank the consultant staff at University College Hospital, London, for permission to publish details of the cases under their care. I am indebted to Mr. A. J. Gardham, Senior Surgeon at University College Hospital, for advice and constructive criticism freely given during the preparation of this paper. The accurate record keeping of Miss Joyce Murray and the medical secretaries of the follow-up department has greatly facilitated the collection of data.

REFERENCES

BILELLO, A., and MONTANINI, N., cited by BURKE (1936).
BILLROTH, C. A. T. (1879), cited by EISENSTAEDT (1938).
BUGHER, J. C. (1934), *Amer. J. Cancer*, **21**, 809.
BURKE, M. (1936), *Ibid.*, **27**, 316.
DELLER, P. J. (1951), *Lancet*, **I**, 1159.
EGLI, F. (1914), *Multiplizität Von Geschwülsten.* Basel: E. Hedinger.
EISENSTAEDT, J. S. (1938), *J. Amer. med. Ass.*, **110**, 2056.
GADE, F. G. (1916), Norwegian Cancer Commission, Oslo Institute.
GLORIAINOWA, R. W., and SCHABAD, L. M. (1931), *Z. Krebsforsch.*, **33**, 594.
HANLON, F. R. (1931), *Amer. J. Cancer.* (Suppl.), **15**, 2001.
HARBITZ, F. (1916), *Beitr. Path. Anat.*, **62**, 503.
HURT, H. H., and BRODERS, A. C. (1933), *J. Lab. clin. Med.*, **18**, 765.
MAJOR, R. H. (1918), *Bull. Johns Hopk. Hosp.*, **29**, 223.
NORBURY, L. E. (1930), *Proc. R. Soc. Med.*, **24**, 198.
PUHR, L. (1926), *Z. Krebsforsch.*, **24**, 38.
SCHREINER, B. F., and WEHR, W. H. (1934), *Amer. J. Cancer*, **20**, 418.
STALKER, L. K., PHILLIPS, R. B., and PEMBERTON, J. D. (1939), *Surg. Gynec. Obstet.*, **68**, 595.
WARREN, S., and GATES, O. (1932), *Amer. J. Cancer*, **16**, 1358.
WHIGHAM, J. R. (1944), *Proc. R. Soc. Med.*, **37**, 233.
WILLIAMSON, T. B. (1950), *Brit. Med. J.*, **I**, 648.

SARCOMA OF THE PENIS

LEIOMYOSARCOMA OF THE PENIS: REPORT OF A CASE WITH A REVIEW OF THE LITERATURE ON SARCOMA OF THE PENIS

By D. J. B. ASHLEY and E. C. EDWARDS

FROM THE UNITED LIVERPOOL HOSPITALS (DAVID LEWIS NORTHERN HOSPITAL)

MALIGNANT connective-tissue tumours of the penis are rare, and a comprehensive search of the literature has revealed accounts of only 54 cases of proven sarcoma of the penis since the description by Beck (1872) of a case of fibrosarcoma affecting this organ. To this series is added the present case of a leiomyosarcoma arising from the subcutaneous tissues of the shaft of the penis in a man aged 67 years.

The most recent review of this subject is by Picatoste (1949), who collected a series of 55 cases from the literature and added one of his own. His series comprised 11 cases of "melanosarcoma", 8 of fibrosarcoma, 1 of rhabdomyosarcoma, 1 of sarcoma "histocitario", 20 which were divided between spindle-celled, round-celled, and polymorphous-celled sarcoma, and 15 instances in which the histological description was insufficient for further classification. We have reclassified these tumours on a histogenetic basis according to the morphology of the tumour cells; there are 20 growths arising from the endothelium of the erectile tissue, 19 fibrosarcomata, 7 cases of Kaposi's sarcoma, 6 (including our own case) of myosarcoma, and 3 tumours of highly malignant and undifferentiated type in which, after consideration of the original description of the histological appearance of the neoplasm together with the photomicrographs, we were unable to come to any decision about the histogenesis of the growth.

In several instances a diagnosis of sarcoma was not substantiated by the description and photomicrographs of the tumour; such cases have been excluded from this series. The earliest account quoted by previous authors, that of Hutchinson (1854), has been omitted, as the report of the case is doubtless that of a benign tumour which, even after incomplete excision, showed no recurrence after the operation and, indeed, Hutchinson referred to it as a fibrocellular tumour and did not suggest it had malignant propensities. Both the cases of Battle (1885) and Mark (1926) were growths consisting of small dark spheroidal cells arising on the glans penis of uncircumcised men; no evidence was adduced to exclude the strong probability that they were undifferentiated carcinomata. Si Mohamed (1888) and Rotthauwe (1952) described lobulated epithelioma and fibro-epithelioma respectively; review of their papers shows that both were in fact epithelial tumours and not sarcoma. The tumour reported as a fibroblastic sarcoma by Hidal and Sadi (1950) had been present for 34 years and was regarded by them as a benign lesion possibly related to Peyronie's disease. Warren and Sommers (1936), Wheelock and Clark (1943), and McDonald and Heckel (1954) described instances of fibrosarcoma arising in the penis in association with epithelioma. While the possibility must be accepted that diploblastic tumours of this type may arise, the mode of origin being by simultaneous malignant neoplasia in the epithelial and connective tissues, proof of such a condition is extremely difficult to establish as there are wide variations in cellular structure in different parts of the same carcinoma. In these cases such proof is not furnished, and the growths are regarded as carcinomata, and *ipso facto* excluded from this series. The 11 cases of malignant melanoma of the penis which were included in Picatoste's (1949) series of 56 cases of penile sarcoma cannot be accepted as mesoblastic tumours (Holmes, 1871; Gould, 1880; Murchison, 1882; Bird, 1885; Fischer, 1887; Miner, 1896; Payr, 1899; Peters, 1922; Colby, 1929; and Wheelock and Clark, 1943 (2 cases)). Whether melanocytes arise by differentiation of the basal-cell layers of the epidermis or derive from cells of the neural crest is still uncertain (Dawson, Innes, and Harvey, 1939; Allen, 1949; Masson, 1951), but in either event malignant tumours of these cells, whether epidermal or neural in origin, are not sarcomata and must be excluded from a discussion of sarcomata in this region.

In several instances reference has been made by other authors to isolated cases said to be instances of sarcoma of the penis. These references have been in the briefest terms and it is profitless to include them in this review. (Sharkey, cited by Battle, 1885; Goldschmidt-Korner, Kapshammer, Pohorecki, and Zakrewsky, cited by Dobrzaniecki, 1930, and Picatoste, 1949.)

The rarity of sarcoma contrasts with the frequency of carcinoma of the penis which, while an uncommon cause of death, is by no means a rare tumour. There were 496 male deaths from penile cancer in England and Wales between 1930 and 1932 (Willis, 1948) compared with 18,876 deaths from carcinomata of the stomach in the same period. Harnett (1952) in the report of the British Empire Cancer Campaign survey of cancer in London found that approximately 1 per cent of cancers in males originated in the penis.

CASE REPORT

J. W. B., a storekeeper aged 67 years, came to hospital complaining of a swelling in the subcutaneous tissues of the penis just behind the glans. The growth had been increasing in size over the previous 12 years; there was no interference with micturition and erection was normal and not painful; the tumour by virtue of its size had been causing difficulty in coitus. At the age of 37 years he had noted a pinhead-sized swelling in the same situation which remained constant in size and did not cause him any trouble for 12 years; it then became ulcerated and began to cause some pain. The swelling was excised in 1937 at another hospital and no record of the operation or the nature of the tumour is available.

A lobulated pinkish-brown tumour 2 cm. × 2 cm. × 1·5 cm. was found in the subcutaneous tissues on the right side of the shaft of the penis just proximal to the coronal sulcus; the skin over one area of the tumour had become ulcerated (*Fig.* 200). The growth was freely mobile, not attached to the deeper structures, and there was no

extension along the penis. The inguinal lymph-nodes were not significantly enlarged.

The patient had been circumcised in infancy and had never suffered from venereal disease. The Wassermann reaction was negative and there was no clinical or radiological evidence of secondary deposits.

AT OPERATION, March 12, 1955 (E. C. E.).—The tumour was excised together with 1·5 cm. of surrounding normal skin and subcutaneous tissue. There was no apparent connexion between the tumour and the fibrous sheath of the corpora cavernosa, and the growth was completely removed.

The patient has been examined at regular intervals for eighteen months since the operation; there has been no evidence of recurrence or of local or distant spread of the growth. The penis is now normal in appearance, there is no dysuria, and coitus is normal.

PATHOLOGICAL REPORT.—The specimen consisted of a firm lobulated tumour 2 cm. × 2 cm. × 1·5 cm. covered by skin which in one small area showed some ulceration. The cut surface showed the 'watered silk' appearance commonly seen in uterine fibroids. Microscopical examination displayed interlacing bands of spindle-shaped cells in which the nuclei assumed the same shape as the cell. Interspersed between these bands were groups of smaller cells with relatively little cytoplasm. The nuclei varied widely in size and shape, the nuclear chromatin was distributed in small aggregations and there were many mitotic figures. Giant nuclei were frequently seen (*Figs.* 201, 202). Preparations stained with Masson's trichrome and phosphotungstic acid hæmatoxylin showed that most of the cells were identifiable as of smooth muscle origin. Myofibrils staining red with Masson's trichrome were to be seen running along the length of the spindle-shaped cells; no cross striations were observed (*Figs.* 203, 204).

The tumour contained few vessels, the majority of which appeared to be veins; these vessels were surrounded by a zone of collagen fibres and their muscle-coats merged with the muscle-tissue of the tumour (*Fig.* 205).

The overlying skin consisted of unaffected squamous epithelium which showed hyperkeratosis and a little subepithelial infiltration by lymphocytes and plasma cells; there was no cytological abnormality in this epithelium, the polarity was normal, prickle cells were present, and there was no nuclear pleomorphism (*Fig.* 206). At the edge of the tumour was an area of normal penile skin with a profuse subcutaneous plexus of small blood-vessels and nerves; normal subcutaneous tissue was also present on the deep surface of the tumour which appeared to have been completely removed. There was no erectile tissue in the material examined. The histological diagnosis was leiomyosarcoma arising in the subcutaneous tissue of the penis.

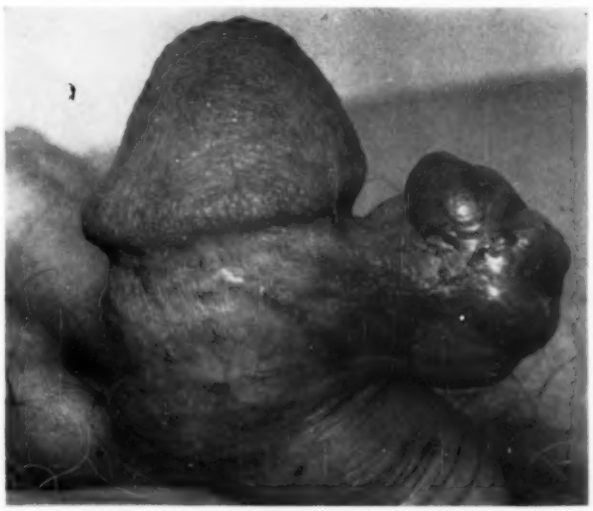


FIG. 200.—Showing the macroscopic appearance of the penis with the tumour in situ.

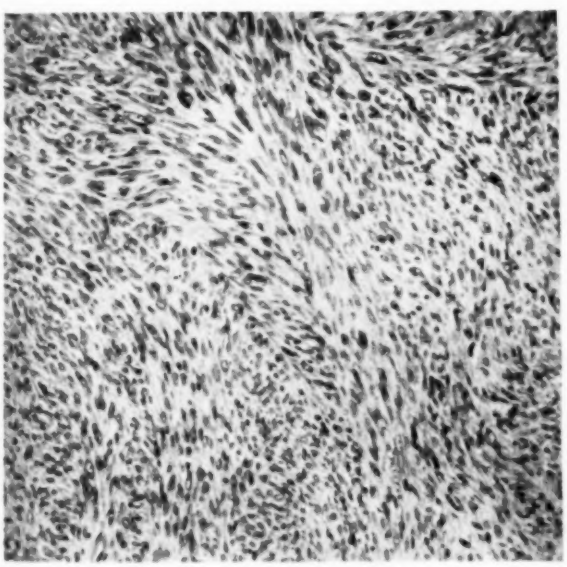


FIG. 201.—Showing the general histological appearance of the tumour with many interlacing bundles of spindle-shaped cells. H. and E. (× 125.)

FIG. 202.—Showing the spindle-shaped tumour cells and giant tumour cells. H. and E. (× 450.)

DISCUSSION

The establishment of the diagnosis of leiomyosarcoma depends on the identification of a malignant process, and also on the identification of cell differentiation as typical of smooth muscle. In this case the criteria of malignancy were the great nuclear pleomorphism, the irregular condensation of the nuclear chromatin into granules, and the presence of

bizarre giant-cell nuclei. The cytoplasm of the cells was typical of that of smooth muscle, the cells were long and ribbon shaped and showed, by specific staining techniques, the presence of longitudinal myofibrils. In this particular instance the tumour arose in the subcutaneous tissue of the penis and probably originated from the smooth-muscle bands

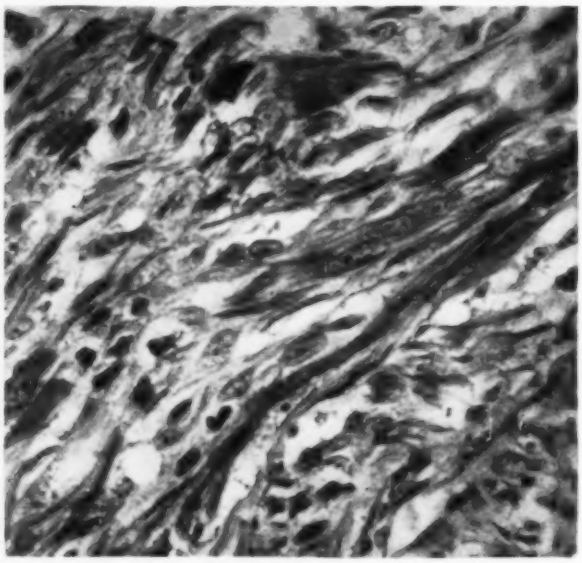


FIG. 203.—Showing longitudinal unstriated myofibrils in the tumour cells. Masson's trichrome. (× 450.)

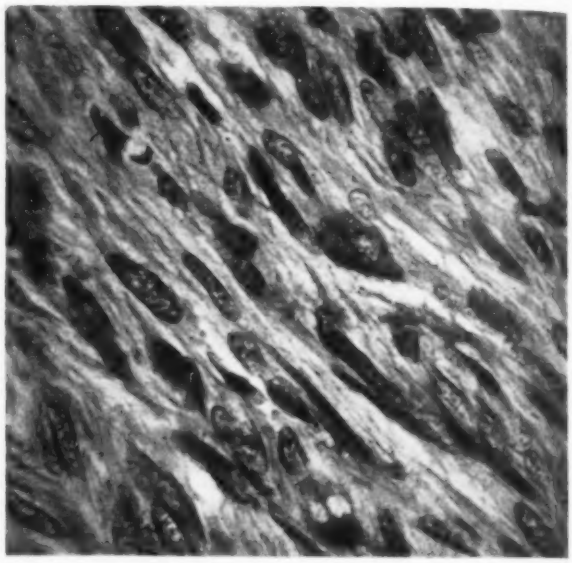


FIG. 204.—Showing longitudinal myofibrils in the tumour cells. Phosphotungstic acid hæmatoxylin. (× 450.)

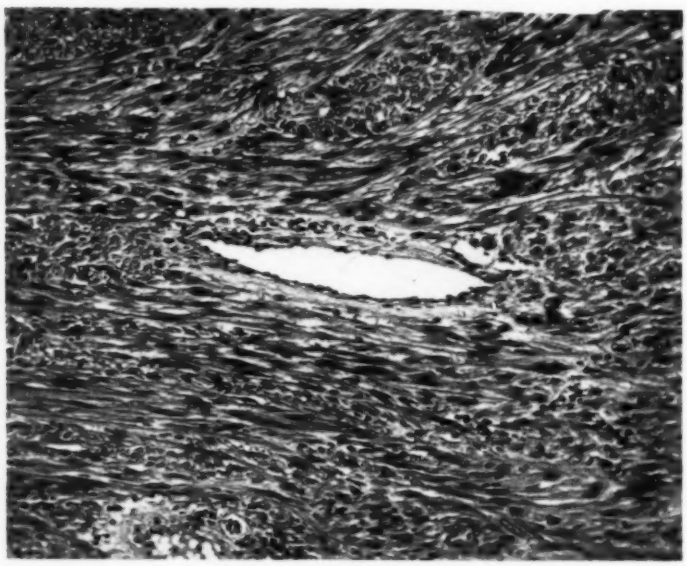


FIG. 205.—Showing a vessel in the substance of the tumour ; the vessel itself is not neoplastic. H. and E. (× 125.)

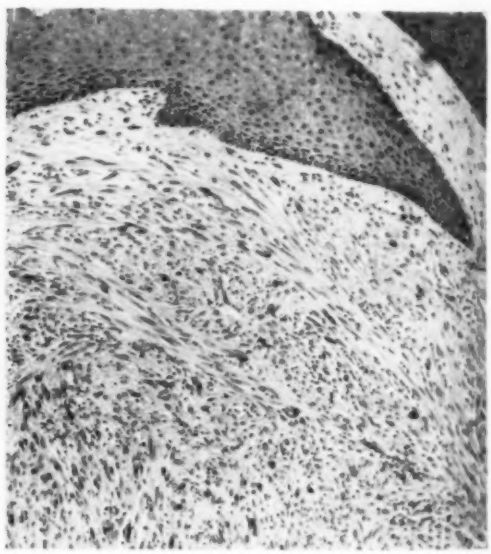


FIG. 206.—Showing the edge of the tumour covered by normal squamous epithelium. H. and E. (× 125.)

to be found in the subcutaneous tissue in this region. The history of a swelling removed from the same site 18 years previously suggests that the present growth is a recurrence of a smooth-muscle neoplasm.

In order to identify the nature of a sarcoma, the degree and type of the differentiation of the tumour cells must be determined to assist the surgeon in determining the form of treatment and in assessing prognosis. Sarcoma may arise from any of the connective tissues of the penis including the perivascular undifferentiated mesenchymal cells of Marchand, and may take one of several morphological forms all differing in their clinical course, degree of malignancy, and therapeutic requirements. Endotheliomata, the most malignant types of sarcoma of the penis, arise in the extensive endothelial lining of the blood-spaces of the erectile tissue or from undifferentiated mesenchymal cells with vasoformative potencies. Fibrosarcoma may arise in the fibrous sheaths and septa of the erectile tissue or in the fibrous element of the subcutaneous tissues. Myosarcomata, either of smooth or striated muscle, arise in the muscular elements of the subcutaneous

tissues or in the sheath of the erectile tissue. The penis may also be involved in a generalized sarcomatous process in the skin—Kaposi's sarcoma. The cases of sarcoma of the penis previously reported in the literature will be considered as they fall into this histological classification.

VASCULAR TUMOURS

Two types of malignant tumour of the vascular tissue of the penis have been described: endothelioma, a malignant tumour arising from the lining cells of the blood-spaces or from undifferentiated vasoformative cells; and Kaposi's sarcoma, a generalized neoplastic condition in which tumours showing organoid differentiation, often to the extent of recognizable tumour blood-vessels, are found in many sites in the skin and also elsewhere in the body. The more highly differentiated type of angiosarcoma in which a solitary lesion of true tumour vessels is found has never been described in the penis.

Endothelioma is one of the most controversial tumours found in oncology. Ewing (1940) in his text-book on neoplastic diseases devotes many pages to this topic, and divides endothelioma into a variety of types according to the site of the cells from which the tumour takes origin or the cell-type towards which differentiation is taking place; he recognizes perivascular, adenoid, and angio-endotheliomata and a diffuse type usually arising from serous membranes. Willis (1948), on the other hand, considers that the lining cells of serous cavities and of blood- and lymph-vessels are derived from fibroblasts and their form is due to environmental factors. He suggests that tumours of these cells will differentiate towards fibroblastic or reticular cells or may form true tumour vessels; in the latter case the tumours should properly be called angiosarcoma. He considers that many of the 'endotheliomata' of serous membranes are secondary carcinomata in which the cells are poorly differentiated.

Many of the reported cases of endothelioma can be shown on critical examination either to be previously unrecognized secondary carcinomata or to show differentiation towards fibroblastic tissue. There remain, however, certain cases in which the tumour cells show unequivocal evidence of differentiation towards endothelial cells. The endotheliomata of the penis fall into this group. They arise either from undifferentiated mesenchymal cells or from the endothelial lining cells of the cavernous spaces of the erectile tissue and fill these spaces without local extension except by intravascular spread along the veins. In many instances clefts lined by tumour cells, which represent malformed tumour capillaries, are present; differentiation into more complex vessels, however, does not take place. This type of tumour has been reviewed by Coppridge, Putnam, and Miale (1946), who collected 12 cases from the literature and added one of their own, and by Waugh (1953), who collected 14 cases from the literature and added 2 of his own. A total of 20 cases appears in the literature, in which the pathological criteria for the diagnosis of endothelioma are substantiated; a summary of these cases is set out in *Table I*. This table includes all the cases presented by Waugh, with the exception of his first case, that of a small nodule in the corpus cavernosum in a man of 53 years; this nodule was found during a routine examination preparatory to another operation, was excised, and on histological examination was proved to consist of well-formed closely-packed capillary vessels lined by endothelial cells which in some areas fused to form a syncytium. This nodule, which was clinically benign, is regarded as an example of a vascular hamartoma, a localized aberration of growth of the blood-vessels without neoplastic significance. It should be considered with the group of angiomatous malformations of the glans penis reported by Mortensen and Murphy (1950). The cases of Tripke (1887), Vopel (1896), Pupovac (1900), Pautrier and Woringer (1935), and Cornwall and Whittaker (1953), which were omitted by Waugh, are included in the present series. The case of Tripke which was accepted by Coppridge and others (1946) as a genuine case of endothelioma was that of a boy aged 16 years, but no clinical details were given. Vopel described a case of round-cell sarcoma of the penis in a man of 41 years. The tumour, which consisted of small round cells filling the cavernous spaces of the corpus spongiosum, caused swelling of the penis and difficulty with micturition; at the time of diagnosis the condition had been present for six months and the inguinal lymph-nodes contained secondary deposits. The patient was treated by amputation of the penis and block dissection of both groups of inguinal lymph-nodes, and was recorded as recovered although no details of the follow-up were given. This case was reviewed by Colmers (1903), who included it in his series of cases of endothelioma, although the possibility of its being an anaplastic carcinoma cannot be excluded completely. Vopel also described 2 patients who died within a few weeks of the diagnosis with extensive lymphadenopathy, but no details of these cases were given, and no further consideration is given to them here.

Pupovac described the case of a man aged 47 years who presented with a generalized swelling of the shaft of the penis which was interfering with coitus. On examination a hard painless growth in the shaft of the penis and regional lymphadenopathy were found. The penis was removed, and bilateral block dissection of the inguinal nodes carried out, as well as laparotomy for removal of lymph-nodes on the internal iliac vessels; death followed within four days of the operation. Histological examination showed the tumour to consist of small round cells which filled the cavernous spaces of the erectile tissue; there was no lesion of the squamous epithelium of the penis. The case of Pautrier and Woringer (1935) was described by them as "sarcome histiocitaire". The lesion began as a swelling on the dorsum of the penis and gradually increased in size to that of a mandarin orange over a period of three months. The tumour consisted of polymorphous cells, some fusiform, some round, with abundant cytoplasm and oval nuclei containing 2–3 nucleoli; mitoses were frequent. There were many malformed capillary vessels in the tumour. The authors regarded the condition as an anaplastic sarcoma of high malignancy; they excluded fibrosarcoma because of the wide variety of cell types present and excluded endothelioma, wrongly we think, because of the lack of vasoformative tissue.

The lesion is analogous to the benign histocytoma or sclerosing angioma (Dawson, 1948).

Cornwall and Whittaker (1953) describe the most recent case of endothelioma in a man of 41 years who complained of painful erections for one year and had noted a painful swelling at the root of his penis for a few days. The tumour was the size of a walnut and was attached to deep structures, but not superficially. Histological examination showed the tumour to consist of low cubical cells filling the vascular spaces; this picture was repeated in the secondary deposits which subsequently developed in the lungs and the local lymph-nodes. The patient was treated by radical amputation of the penis and block dissection of the inguinal lymph-nodes, followed by post-operative irradiation. Death ensued 14 months after the operation, 2 years and 2 months after the onset of the disease.

In the present series the youngest patient was 10 months old and the oldest 75 years old, but 12 of the 19 cases in which the age was recorded were between 40 and 60 years of age. The presenting symptom was a tumour of the penis in 5 cases, priapism or painful erection in 6, generalized swelling of the penis in 3 and pain, dysuria, and the symptoms of generalized metastasis in 1 case each. In the case described by Tripke no clinical information was given. The question of malignancy in these tumours was considered by Waugh (1953), who divided the recorded cases into three groups: (1) Endothelioma infantum, a subdivision which is not considered justifiable as the 2 cases which he placed in this group are distinguished only by the age of onset; (2) Benign endothelioma, in which group he places the cases of Alexander and Dunham (1897), Hildebrand (1898), Balog and Cerqua (1930), Dobrzaniecki (1930), and his own *Case* 1, all of which recovered; and (3) Malignant endothelioma. Malignancy is, however, a term which has a largely clinical connotation. The pathological criterion for

Table I.—ENDOTHELIOMA

AUTHOR	AGE OF PATIENT	INITIAL SYMPTOMS	SITE OF TUMOUR	TREATMENT	COURSE
Maurer (1883)	50	Priapism 3 mth. Enlarged inguinal nodes	Corpora cavernosa	Nil	Died 1 mth. after diagnosis
Tripke (1887)	16	No clinical details			
Vopel (1896)	41	Swelling of penis 6 mth. Dysuria	Corpus spongiosum	Amputation and block dissection	Not stated
Alexander and Dunham (1897)	50	Tumour of penis 6 mth.	Corpus cavernosum	Local excision	No recurrence for 27 mth. Died 3 yr. after operation. No post-mortem
Hildebrand (1898)	68	Tumour of penis 1 yr.	Under surface of penis	Local excision	Free of recurrence 6 mth. after operation
Pupovac (1900)	47	Swelling of penis 6 mth.	Corpora cavernosa	Amputation and block dissection	Died 6 mth. after operation
Colmers (1903)	56	Priapism 2 mth.	Corpora cavernosa	Amputation	Died 1 wk. after operation
Creite (1905)	2	Priapism 2 wk.	Corpora cavernosa	Amputation	Died 3 mth. after operation
Migliorini (1905)	50	Tumour of glans 18 mth.	Glans penis	Local excision	Not followed
Pelagatti (1910)	65	Uræmia. Nodules of penis 1 yr.	Corpora cavernosa	Nil	Died 1 wk. after admission
Gobbi (1922)	10 mth.	Generalized swelling of penis	Corpora cavernosa	Nil (biopsy only)	Died a few days after biopsy
Balog and Cerqua (1930)	40	Pain at root of penis. Small tumour 2 yr.	Crus penis	Amputation	Free of recurrence 5 mth. after operation
Dobrzaniecki (1930)	59	Dysuria. Tumour in glans 1 yr.	Glans penis	Amputation	Free of recurrence 4 mth. after operation
Nagayo (1930)	24	Tumour of penis	Crus penis	Local excision	Died in 6 mth. from start of illness with widespread metastases
Yamamoto (1930)	58	Priapism 6 mth.	Crus penis	Amputation	Died 7 mth. after operation
Pautrier and Woringer (1935)	—	Tumour in dorsum of penis 3 mth.	Corpora cavernosa	Not stated. (Biopsy only ?)	Not stated
Foulds and Flett (1938)	45	Symptoms of metastases	Corpora cavernosa	Nil	Died 3 wk. after admission, 9 mth. after start of illness
Coppridge, Putnam, and Miale (1946)	58	Tumour on corona 9 mth.	Glans penis	Radical amputation and irradiation	No recurrence 5 mth. after operation
Cornwall and Whittaker (1953)	41	Priapism 12 mth.	Crus penis	Radical amputation and irradiation	Died 14 mth. after operation, widespread metastases
Waugh (1953)	75	Pain at root of penis. Generalized swelling of penis	Crus penis	Irradiation and radical amputation	Died 13 mth. after operation

the diagnosis of malignancy—invasion of the surrounding tissues—is mainly of use when consideration is being given to epithelial tumours which arise from tissues having a clearly defined normal locus. Tumours of connective tissue and especially of the vasoformative tissues are much less susceptible to histological grading and the borderline between benign and malignant tumours is much less well defined. It is impossible to make a retrospective histological diagnosis of a benign tumour and, with the exception of Waugh's first case which is regarded as a hamartoma rather than a true neoplasm, all of these tumours should be placed in one group. Endothelioma is usually of high malignancy. In 17 of the cases follow-up details were recorded; 11 of the patients died, the longest duration of the whole illness, including operative treatment, being 23 months, while in the 4 cases where no definitive treatment was undertaken the survival time was 3, 4, 7, and 9 months respectively. Five patients are recorded as having survived operation and were alive and free from recurrence 16–29 months after the onset of symptoms. One of these patients, a case of Alexander and Dunham, died 3 years after the operation, 3 years and 5 months after the onset of symptoms, but no details of the cause of death are available; he had been free from recurrence when seen by the authors 9 months previously. In the remaining 4 instances the tumour was in the distal part of the penis and in 3 of the 4 the presenting sign was a swelling in the penis. All tumours were small and were treated by local operation instituted without delay; in one instance post-operative irradiation was administered as well. The fourth patient, Dobrzaniecki's case, presented complaining of deviation of the urinary stream, dysuria, and pain in the penis. The organ was amputated and the patient was free from recurrence 4 months later. Only 1 of the patients who were successfully treated had a lesion at the root of the penis; this was the patient of Balog and Cerqua and he complained of pain at the root of the penis which had been present for 2 years. On examination a pea-sized nodule was found; local excision of this resulted in an apparent cure. The patient was free of symptoms and recurrence 5 months after the operation.

From this series it seems that endothelioma of the penis is a malignant condition and that the prognosis depends on the site of the lesion as well as on the rapidity with which the patient presents himself for surgery. Those cases which presented with a localized swelling in the distal part of the penis have done well, while those who exhibited generalized swelling of the penis or presented with priapism and pain on erection have all died within a short period of time, despite treatment.

The patients who present with a localized tumour in the penis are best treated by local excision or partial amputation of the penis. The operation should be followed by careful observation of the patient and prompt treatment of any recurrence. Those who suffer from generalized swelling of the penis and in whom the diagnosis of malignant endothelioma has been confirmed by biopsy should be treated on the same general lines as cases of other highly malignant soft-tissue sarcomata. A course of pre-operative irradiation should be followed by radical amputation and block dissection of the inguinal lymph-nodes. The prognosis in such a case is of course very poor.

KAPOSI'S SARCOMA

The condition, first described by Kaposi (1872), is a malignant tumour of the vasoformative tissues. Up to the present over 600 cases have been described with a wide range of clinical and histological variations. A typical case presents as a single blue-red macula which shows dilated veins in the dermis surrounded by a zone of infiltration with lymphocytes and plasma cells; the lesion then progresses through a granulomatous phase in which there is endothelial proliferation with the formation of imperfect vascular sinuses from which there may be extravasation of blood into the tissue spaces; the final phase is one of frank sarcoma of the spindle-cell type interspersed by hæmangiomatous elements. The initial macule, situated usually on the lower limb, gradually extends and further lesions appear in the skin, and later in the gastro-intestinal tract, lymph-nodes, and heart. Kaposi's sarcoma of the penis has only been described 7 times in the literature. Barringer and Dean (1935) described 2 cases in which the initial lesion was on the glans penis and in both instances the lesion was treated by local excision accompanied in one case by post-operative irradiation. These patients survived without local recurrence and without the development of further lesions for periods of 6 and 14 months; this period is of course too short for any claim of cure to be made. McCarthy and Pack (1950) made reference to 3 cases in which the initial lesion appeared on the penis; in 2 of these cases local excision of the lesion was carried out and the two patients were free of further lesions after 5 and 6 years respectively; no details of the third case were given. Hopkins and Hudson (1953) and Low, Coakley, and Shenting (1954) described cases in which the penile lesion was accompanied by similar lesions elsewhere. In the case reported by Hopkins and Hudson the course of the disease was chronic and the patient was alive, although with extensive lesions, 9½ years after the onset; the case of Low and others, on the other hand, showed a much more rapid course and death ensued in a little over a year. The details of these cases are summarized in *Table II*.

Kaposi's sarcoma, a generalized disorder, is included in a discussion on sarcoma of the penis because of the differential diagnosis when the initial lesion appears on the penis, and also because of the good results obtained in the 5 cases where the initial lesion on the penis was removed *in toto*. Two of these cases are among the only three patients in McCarthy and Pack's series of 36 cases of Kaposi's sarcoma who were alive and free from lesions 5 years after the onset of the disease.

FIBROSARCOMATA

Tumours of fibroblastic tissue range from benign tumours in which there is extensive formation of dense collagenous tissue to highly cellular tumours in which there is little or no production of collagen. In general the degree of malignancy of a fibrous-tissue tumour may be assessed by histological criteria, the more malignant tumours showing wide diversity of

Table II.—KAPOSI'S SARCOMA

AUTHOR	AGE OF PATIENT	SITE OF LESION	TREATMENT	COURSE
Barringer and Dean (1935). *Case* 1	45	Glans	Partial amputation. Irradiation	Well, with no further lesions 6 mth. after operation
Barringer and Dean (1935). *Case* 2	56	Glans	Local amputation	Well, with no further lesions 14 mth. after operation
McCarthy and Pack (1950). *Case* 1	Not stated	Glans	Local excision	Well, with no further lesions 5 yr. after operation
McCarthy and Pack (1950). *Case* 2	Not stated		Local excision	Well, with no further lesions 6 yr. after operation
McCarthy and Pack (1950). *Case* 3	Not stated		Nil	One manifestation of generalized disease
Hopkins and Hudson (1953)	53			Generalized lesions one of which was on the penis. Alive 10 yr. after onset of illness
Low, Coakley, and Shenting (1954)	20	Right corpus cavernosum	Nil	Similar lesions were present elsewhere, death ensued 8 mth. after diagnosis, 12 mth. after onset

Table III.—FIBROSARCOMA

AUTHOR	AGE OF PATIENT	SITE OF TUMOUR	DURATION BEFORE TREATMENT	TREATMENT	COURSE
Beck (1872)	56	Glans penis	13 yr.	1. Local excision 2. Amputation	Recurrence 2 yr. after operation. No follow-up after second operation
Porter (1882)	44	Shaft of penis	6 mth.	Local excision	Died of post-operative complications. No secondary deposits were present
Battle (1889), (1892)	50	Crus penis	2 yr.	1. Local excision 2. Excision of recurrence	Recurrence 4 yr. after operation. Died 1 yr. after second operation with pulmonary secondaries
Fenwick (1889)	36	Crus penis	3½ yr.	1. Local excision 2. Local excision	Recurrence 2 yr. after operation. Well and free from recurrence 6 mth. after second operation
MacCormac (1895)	64	Root of penis	6 mth.	Amputation and castration	Died of post-operative complications. No secondary deposits were present
Key (1903)	74	Glans penis	4 yr.	1. Local excision 2. Amputation	Recurrence 3½ yr. after operation. No further follow-up
Galt (1911)	60	Shaft of penis	8 mth.	Amputation and block dissection	Died 2 mth. after operation. Secondary deposits present
Heigel (1913)	32	Shaft of penis	1½ yr.	Amputation and block dissection	No follow-up
Peraire (1919), (1920)	43	Shaft of penis	1½ yr.	1. Local excision 2. Amputation	Recurrence 14 mth. after operation. No recurrence 1 yr. after second operation
Joelsen (1924)	57	Glans penis	2 yr.	Amputation and block dissection	No recurrence 8 mth. after operation
Evans (1931)	44	Shaft of penis	5 yr.	Local excision	No follow-up
Hval (1935)	63	Glans penis	3 mth.	Amputation	No follow-up
Gaudin (1941)	31	Shaft of penis	5 yr.	1. Local excision 2. Local excision	Recurrence 4 yr. after operation. No recurrence 5 mth. after second operation
Levant (1944)	29	Shaft of penis	16 mth.	Irradiation	Died 14 mth. after diagnosis
Leveuf (1944)	6½	Shaft of penis	—	Local amputation and irradiation	No recurrence 2 yr. after operation
Wattenberg (1944)	65	Glans penis	2 yr.	Partial amputation	No follow-up
Picatoste (1949), (1956)	5	Glans penis	1 mth.	Local excision, block dissection	No recurrence 6 yr. and 8 mth. after operation
Fuentes-Ferrer (1950)	30	Glans penis	5 mth.	Partial amputation, block dissection, and irradiation	No recurrence 3 mth. after operation
Haines and Garvey (1952)	27	Shaft of penis	—	Amputation	No follow-up

cell type, although in all cases some, or most, of the cells retain a spindle shape associated with little or no collagen formation. In general, fibrosarcomata are clinically of relatively low malignancy, about 8 per cent of the tumours diagnosed histologically as fibrosarcoma developing metastases, but there is a marked tendency to local recurrence after inadequate treatment.

Fibroblastic tumours form the second largest group of sarcomata of the penis. In all there are 19 instances of fibrosarcoma of the penis in the literature. Details of these cases are summarized in *Table III*. The age incidence was similar to that of endotheliomata, ranging from 5 to 74 years, but the majority of cases occurred in the fourth to the seventh decades. The initial symptom in all cases was a localized swelling of the penis, in 7 instances of the glans, in 9 of the shaft, and in 3 of the root of the penis. The clinical course in these cases has been favourable much oftener than in the series of cases of endotheliomata; 3 patients only have died as a result of the tumour. The patient of Galt (1911) died 2 months after amputation of the penis and block dissection of the inguinal lymph-nodes; this was a highly malignant growth and secondary deposits were present in the lymph-nodes at the time of diagnosis. The patient of Battle (1889, 1892) died from a recurrence 4 years after an initial local excision of a tumour in the crus penis, and Levant (1944) described a young man of 29 years suffering from fibrosarcoma who refused all operative treatment and died 14 months after diagnosis despite irradiation. In 2 cases, those of Porter (1882) and MacCormac (1895), the patients died of post-operative complications within a few days of operation; post-mortem examination revealed no evidence of a secondary deposit in either case. In 6 cases the tumour recurred 1–4 years after local excision. Five of these recurrences were adequately treated by further local excision or by amputation, and the patients remained well and free from further recurrence for further periods of 6 months to 5 years. The treatment of choice for these patients is a local excision of the lesion, or, if this is not possible owing to the size and situation of the growth, a partial amputation alone should suffice.

Two cases presented interesting histological features; Haines and Garvey (1952) report the case of a man aged 27 years who had suffered from generalized neurofibromatosis all his life and had lately noticed a rapid increase in size of one of the nodules on the penis, this nodule was diagnosed histologically as a neurosarcoma arising from the nerve-sheath; unfortunately no follow-up was reported. The case of Levant (1944), also of a young man, was described as a sarcoma, probably reticulum-cell type, by a panel of the American Society of Clinical Pathologists, but the photomicrographs of the tumour, which showed spindle cells in bundles and giant cells, justifies its inclusion in this group.

MYOSARCOMATA

Sarcomata showing differentiation towards muscle-cells form the smallest group of malignant mesenchymal tumours of the penis. Five cases are recorded in the literature, 2 of rhabdomyosarcoma and 3 of leiomyosarcoma. Henke and Lubarsch (1928) found in the collection of the Vienna Pathological Institute a case of rhabdomyosarcoma of the penis. The patient, a man 40 years old, presented himself to the surgical clinic in 1837; no clinical details are available except that the patient subsequently came to post-mortem examination. The tumour arose in close relation to the corpora cavernosa just proximal to the fossa navicularis and had extended through the penis and also metastasized to the regional lymph-nodes. Histological examination showed it to be a malignant connective-tissue tumour and to contain well-defined striated muscle-fibres which are well shown in the photomicrographs. A similar histological picture was seen in the secondary deposits in the lungs. The other rhabdomyosarcoma, that of Puhl (1929), was a tumour the size of a walnut occurring in the corpus spongiosum of a child; it consisted largely of spindle cells, but a few differentiated striated muscle-fibres were also present. This patient was treated by local excision of the tumour; unfortunately no record of the post-operative course was given.

The 3 cases of leiomyosarcoma were reviewed by Meller (1932), who described one case of his own and quoted the cases of Kreibig (1931) and of Levi (1930). Levi described a man of 38 years who had had a small nodule on the penis since childhood. This swelling had caused no discomfort until, one year before he attended the clinic, it began to increase in size. A large, hard, lobulated tumour was seen on the dorsum of the penis; it was freely mobile and was not attached to the overlying skin which, apart from a small erosion, appeared normal. Local excision of the tumour was carried out; on histological examination large numbers of interlacing spindle-shaped cells were seen, mitoses were frequent, and there were many tumour giant cells. Levi regarded the growth as a fibrosarcoma, but Meller, on the basis of the clinical history and the presence of many tumour giant cells, considered it to be a smooth-muscle sarcoma. No detail of the post-operative course was given.

Kreibig (1931) described a tumour arising on the dorsum of the penis in a man aged 46 years. At the age of 12 years this patient had had a small nodule removed from the prepuce and at the age of 39 years further small nodules were removed; histological examination of these nodules was not undertaken. Six years later he presented with a hard solid plaque 1·5 cm. in diameter which was situated in the subcutaneous tissue of the dorsum of the penis; the plaque was removed and was diagnosed microscopically as a fibroma. The patient was symptom-free for a further 8 months, when he was seen again with a hard swelling in the distal part of the shaft of the penis; irradiation had no effect on the tumour, and the penis was amputated. The specimen showed multiple, hard, grey-white nodules in the whole length of the penis; on section these proved to consist of spindle cells arranged in interlacing bundles, the cell nuclei were elongated, and there were many polygonal cells between the bundles. Specific staining techniques showed the tumour cells to be smooth-muscle cells. The growths infiltrated into the surrounding connective tissue and into the spaces of the corpora cavernosa and the corpus

spongiosum. No clinical details of the subsequent course of this patient were given.

The case described by Meller (1932) was of a man aged 64 years complaining of a tumour of his penis, dysuria, and hæmaturia. Clinically the growth was thought to be an angioma and after a course of irradiation a radical amputation of the penis was performed. The tumour, which was 4 cm. in diameter, was situated in the subcutaneous tissues just proximal to the coronal sulcus; it was of a uniform firm fibrous consistency. It consisted of many interwoven spindle cells with a few tumour giant cells; many mitotic figures were present and the edge of the tumour infiltrated the surrounding connective tissue. The tinctorial reactions of the tumour were typical of leiomyosarcoma. Details of these 5 cases together with our own case are given in *Table IV*.

Table IV.—MYOSARCOMA

AUTHOR	AGE OF PATIENT	SITE OF LESION	TREATMENT	COURSE
Rhabdomyosarcoma				
Henke and Lubarsch (1928)	40	Shaft	Not stated	Died, secondary deposits in lungs
Puhl (1929)	Child	Shaft	Local excision	No follow-up
Leiomyosarcoma				
Levi (1930)	38	Shaft	Local excision	No follow-up
Kreibig (1931)	46	Shaft	Amputation	No follow-up. This tumour was itself a third recurrence; two nodules had been removed 24 and 6 yr. previously
Meller (1932)	64	Shaft	Radical operation after irradiation	No follow-up
Ashley and Edwards (1957)	67	Shaft	Local excision	Alive and free of recurrence 1 yr. 6 mth. after operation. This tumour was itself a recurrence of a nodule removed 18 yr. previously

It is unfortunate that in the case of the two rhabdomyosarcomata there is very little clinical detail; it is known, however, that one of these cases came to post-mortem examination and that in the other the number of differentiated elements was small. It is well known that rhabdomyosarcomata are of high malignant potential and show a poor response to radiotherapy (Cade, 1951). The treatment, therefore, is radical surgical removal of the tumour.

The cases of leiomyosarcoma show many less malignant propensities. Three of the 4 cases presented with the typical history of recurrent nodules in the penis over a long period without evidence of metastasis. The treatment of this condition is wide local excision if the site and the size of the tumour lend themselves to such an operation, or, if not, partial amputation of the organ.

UNDIFFERENTIATED TUMOURS

The cases of Koehler (1880) and Webber (1905) could not be classified into the groups of differentiated tumours as insufficient information was available in the reports and there were no photomicrographs. Both neoplasms were highly malignant round-celled tumours which recurred after excision and were associated with widespread metastases. In neither case were the clinical history or the histological findings suggestive of endothelioma or fibrosarcoma, although sufficient detail was given for the tumours to be accepted as sarcomata. Such growths must be regarded as highly malignant anaplastic sarcomata of uncertain origin.

The case described by Vintici and Alterescu (1934) must also be considered separately as the diagnosis of sarcomata was made on clinical grounds only; histological examination was not carried out because of the hæmorrhagic state of the specimen, but there was no lesion in the skin of the penis or prepuce. The patient was aged 22 years and presented with a 6-months' history of penile pain and priapism. The lesion, which affected the corpora cavernosa only, was regarded by the authors as a round-cell sarcoma on the grounds that a fibrosarcoma would have formed a localized tumour and that endothelioma would have invaded all the cavernous tissue. The response to radiotherapy was poor; operative treatment was not undertaken as there were metastases present at the time of diagnosis.

SUMMARY AND CONCLUSIONS

A series of 54 cases of sarcoma of the penis has been collected from the literature and one further case added. The tumours have been classified according to the morphology of the cells, and the clinical course in each group reviewed.

Twenty of the tumours were classified as endothelioma. In this group the majority, which were clinically highly malignant tumours, presented with priapism or with generalized swelling of the penis; a minority presented with localized tumours of the penis. In the former group no treatment holds out much hope of a cure, but we consider that radical amputation of the penis preceded and followed by radiotherapy is the treatment of choice. In the group of patients complaining of a localized swelling we consider that the initial treatment should be a wide local excision followed by careful observation at the follow-up clinic.

Seven cases of Kaposi's sarcoma affecting the penis have been described. In those in which the initial lesion was on the penis local excision of the lesion has been followed by remission of the disease and this should be the treatment of choice; in the remaining cases where the penile lesion is only part

of a generalized disease no specific local treatment can be recommended.

Nineteen cases were classified as fibrosarcomata. These tumours, all of which presented as swellings in the penis, were of much lower malignancy than the endotheliomata. Local excision of the tumour and of any recurrence is an adequate method of treatment.

The myosarcomata are too few for any dogmatic line of treatment to be recommended. In the case of the 2 rhabdomyosarcomata the lesions were of high malignancy and extensive amputation should therefore be undertaken; in contrast, leiomyosarcomata were of low malignancy and, as in the case of fibrosarcoma, extensive local excision should be undertaken.

The remaining 3 cases in which identification of the type of tumour was not possible were all highly malignant tumours and treatment was of no avail. It is probable that, with the methods now available for histological diagnosis, identification of the type of tumour would be possible and that guidance in treatment could thereby be given.

In the case of sarcoma of the penis it is desirable, if possible, that the initial operation should be a wide local excision of the tumour and that the subsequent treatment should be guided by identification of the particular type of sarcoma which is present.

Acknowledgements.—We wish to express our thanks to Mr. Philip Hawe, under whose care this patient was admitted to hospital, for permission to publish this case.

REFERENCES

ALEXANDER, S., and DUNHAM, E. K. (1897), *J. cutan. Dis.*, **15**, 247.
ALLEN, A. C. (1949), *Cancer*, **2**, 28.
BALOG, P., and CERQUA, S. (1930), *Arch. Derm. Syph., Wien*, **161**, 86.
BARRINGER, B. S., and DEAN, A. L. (1935), *Trans. Amer. Ass. gen. urin. Surg.*, **28**, 409.
BATTLE, W. H. (1885), *Lancet*, **1**, 520.
— — (1889), *Ibid.*, **1**, 513.
— — (1892), *Trans. path. Soc. Lond.*, **44**, 104.
BECK, M. (1872), *Ibid.*, **24**, 153.
BIRD, G. (1885), *Lancet*, **1**, 520.
CADE, S. (1951), *Proc. R. Soc. Med.*, **44**, 19.
COLBY, F. H. (1929), *New Engl. J. Med.*, **201**, 924.
COLMERS, F. (1903), *Beitr. path. Anat.*, **34**, 295.
COPPRIDGE, W. M., PUTNAM, G. H., and MIALE, J. B. (1946), *J. Urol.*, **56**, 112.
CORNWALL, W. D., and WHITTAKER, L. (1953), *Ibid.*, **69**, 307.
CREITE (1905), *Dtsch. Z. Chir.*, **79**, 299.
DAWSON, E. K. (1948), *Edinb. med. J.*, **55**, 655.
— — INNES, J. R. M., and HARVEY, W. F. (1939), *Ibid.*, **46**, 695.
DOBRZANIECKI, W. (1930), *J. Urol. méd. chir.*, **29**, 368.
EVANS, A. (1931), *Proc. R. Soc. Med.*, **25**, 329.
EWING, J. (1940), *Neoplastic Diseases*, 4th ed., 335. Philadelphia: W. B. Saunders.
FENWICK, E. H. (1889), *Lancet*, **2**, 1060.
FISCHER, G. (1887), *Dtsch. Z. Chir.*, **25**, 313.
FOULDS, G. S., and FLETT, R. H. (1938), *J. Urol.*, **40**, 826.
FUENTES-FERRER, J. J. (1950), *Arch. Hosp. univ. Habana*, **2**, 335.
GALT, H. M. (1911), *Lancet*, **2**, 217.
GAUDIN, H. (1941), *N.Z. Med. J.*, **40**, 188.
GOBBI, L. (1922), *Policlinico*, **29**, 23.
GOULD, A. P. (1880), *Lancet*, **1**, 438.
HAINES, C. E., and GARVEY, F. K. (1952), *J. Urol.*, **63**, 542.
HARNETT, W. L. (1952), *Survey of Cancer in London*, 2. London: British Empire Cancer Campaign.
HEIGEL, A. (1913), *Prag. med. Wschr.*, **38**, 583.
HENKE, F., and LUBARSCH, O. (1928), *Handbuch der spezialen Pathologischen Anatomie und Histologie*, **6**, 369. Berlin: J. Springer.
HIDAL, M. T., and SADI, A. (1950), *Rev. paulist. Med.*, **36**, 101.
HILDEBRAND (1898), *Dtsch. Z. Chir.*, **48**, 209.
HOLMES, T. (1871), *Trans. path. Soc. Lond.*, **23**, 157.
HOPKINS, J. A., and HUDSON, P. B. (1953), *Brit. J. Urol.*, **25**, 233.
HUTCHINSON, J. (1854), *Trans. path. Soc. Lond.*, **6**, 228.
HVAL, E. (1935), *Norsk. Mag. Lægevidensk.*, **96**, 153.
JOELSEN, J. J. (1924), *Surg. Gynec. Obstet.*, **38**, 150.
KAPOSI, M. (1872), *Arch. Derm. Syph., Wien*, **4**, 265.
KEY, A. (1903), *Hygiea, Stockh.*, **3**, 589.
KOEHLER, R. (1880), *Charité-Ann.*, **5**, 607.
KREIBIG, W. (1931), *Dtsch. Z. Chir.*, **231**, 277.
LEVANT, B. (1944), *J. Urol.*, **52**, 63.
LEVEUF, J. (1944), *Arch. franç. Pédiat.*, **2**, 209.
LEVI, I. (1930), *G. ital. Derm. Sif.*, **71**, 1559.
LOW, H. T., COAKLEY, H. E., and SHENTING, W. C. (1954), *J. Urol.*, **72**, 886.
MCCARTHY, W. D., and PACK, G. T. (1950), *Surg. Gynec. Obstet.*, **91**, 465.
MACCORMAC, W. (1895), *Clin. J.*, **7**, 130.
MCDONALD, J. H., and HECKEL, N. J. (1954), *J. Amer. med. Ass.*, **154**, 993.
MARK, E. G. (1926), *J. Urol.*, **15**, 611.
MASSON, P. (1951), *Cancer*, **4**, 9.
MAURER, M. (1883), Inaugural Dissertation. Halle.
MELLER, H. (1932), *Wien. Klin. Wschr.*, **45**, 49.
MIGLIORINI, G. (1905), *G. ital. Mal. vener.*, **40**, 278, 445.
MINER, C. H. (1896), *Univ. med. Mag. Pa. Univ.*, **9**, 824.
MORTENSEN, H., and MURPHY, L. (1950), *J. Urol.*, **64**, 396.
MURCHISON (1882), cited by GROSS, S. D. (1882), *System of Surgery*, 6th ed., **2**, 834. Philadelphia.
NAGAYO, M. (1930), quoted by WAUGH (1953), *Dr. Muira Moriji, 25th Anniversary Volume of Collected Papers.*
PAUTRIER, L. M., and WORINGER, F. (1935), *Bull. Soc. franç. Derm. Syph.*, **42**, 826.
PAYR, E. (1899), *Dtsch. Z. Chir.*, **53**, 221.
PELAGATTI, M. (1910), *Derm. Stud., Hamburg*, **20**, 318.
PERAIRE, M. (1919), *Paris chir.*, **11**, 57.
— — (1920), *Ibid.*, **12**, 278.
PETERS, W. (1922), *Z. Urol.*, **11**, 57.
PICATOSTE Y PATINO J. (1949), *Arch. esp. Urol.*, **5**, 316.
— — (1956), personal communication.
PORTER, W. G. (1882), *Trans. path. Soc. Philad.* (1879–81), **10**, 142.
PUHL, H. (1929), *Z. Urol.*, **23**, 583.
PUPOVAC, D. (1900), *Dtsch. Z. Chir.*, **58**, 586.
ROTTAHAUWE, G. (1952), *Beitr. Klin. Chir.*, **184**, 41.
SI MOHAMED, F. (1888), *Art. Méd.*, **24**, 113.
TRIPKE, A. (1887), Inaugural Dissertation. Wuerzburg.
VINTICI, V., and ALTERESCU, H. (1934), *J. Urol. méd. chir.*, **38**, 27.
VOPEL, W. (1896), Inaugural Dissertation. Halle.
WARREN, S., and SOMMERS, G. N. J. (1936), *Arch. Surg., Chicago*, **33**, 425.
WATTENBERG, C. A. (1944), *J. Urol.*, **51**, 543.
WAUGH, T. R. (1953), *Arch. Path. Lab. Med.*, **55**, 98.
WEBBER, H. W. (1905), *Brit. med. J.*, **2**, 1587.
WHEELOCK, M. C., and CLARK, P. J. (1943), *J. Urol.*, **49**, 478.
WILLIS, R. A. (1948), *Pathology of Tumours*, 642, 576. London: Butterworth.
YAMAMOTO, K. (1930), *Jap. J. Derm. Urol.*, **30**, 50.

RECTAL LYMPHOGRANULOMA VENEREUM

By R. P. M. MILES, Jamaica

Lymphogranuloma venereum is a disease of world-wide distribution with a specially high incidence amongst coloured peoples. It has been described in places as far apart as Western Australia and north-eastern Canada. It is common in Europe, although the incidence in the United Kingdom is still surprisingly low. With the advent of large numbers of West Indian immigrants, both male and female, to Britain, there appears to be a definite danger of widespread dissemination of this very highly infective disease. During a recent survey in Jamaica of the incidence of lymphogranuloma venereum, no less than one-third of three groups of persons employed in large industrial concerns who were tested showed a positive complement-fixation test (Sigel, 1954). The more chronic manifestations of the disease, at present extremely rare in Britain, are likely to appear in increased numbers as the disease process advances in those who have already acquired the infection before immigration. It is opportune therefore to review the anorectal manifestations of the disease and to describe our experience in the management of a series of ninety-one cases seen in the University College Hospital of the West Indies in the first three years since its opening in September, 1952.

HISTORICAL REVIEW

As with so many aspects of disease, credit for the first mention of lymphogranuloma as a separate entity can be given to John Hunter (1786), who in his *Treatise on Venereal Disease* described a condition in which buboes developed, but were not preceded by a chancre and were unaffected by mercury. Durand, Nicholas, and Favre in 1913 gave the first accurate description of the disease. Frei in 1925 introduced his intradermal test which made diagnosis possible, while the virus was isolated by Hellerstrom and Warsen in 1930. Levaditi, Ravant, and Schoen in 1932 transmitted the disease to mice by the intracerebral route, and Findlay (1933) in England described the virus and its life-cycle in more detail.

The anorectal type of disease was first identified as being caused by lymphogranuloma venereum by Bensaude and Lambling of Paris in 1936, who, in a stimulating paper given to the Royal Society of Medicine, described 158 cases. It is surprising how little interest this paper aroused in England, judging from the paucity of accounts of the disease up to the present time, not more than 7 cases being published. Hawe (1951) described 2 cases and cited 5 other cases recorded by Naunton Morgan (1937, 2 cases), Batchelor (1937), Lewis (1941), and Pringle (1940) (1 case each).

Many large series have been published in America, Martin (1933) describing 227 cases of rectal strictures in Negro women; Grace (1941) analysing 128 cases of anorectal disease; Spiesman, Levy, and Brotman (1937), 183 cases; and Woods and Hanlon (1944), 192 cases.

Papers dealing specifically with the surgical aspects of the disease and its treatment have been very numerous in the last twenty years. Credit, however, must be given to Henri Hartmann of Paris for presenting, as early as 1922, a careful personal study of 86 inflammatory strictures of the rectum and describing his operation of intrasphincteric amputation of the rectum performed on 35 cases. The aetiology of the disease was unknown at that time and Hartmann could commit himself no further than stating "sex has certainly an influence on the production of these strictures".

Bacon (1941) described the surgical treatment of 24 cases, advocating a two-stage perineal resection of the rectum with permanent colostomy. Woods and Hanlon (1944) analysed 192 cases, of which 35 were treated by rectosigmoid resection; 108 cases were treated by rectal dilatation with only fair results. They also drew attention to the risk of squamous-celled carcinoma arising in the stricture, 3 cases having been seen in their series. Wright, Berg, Bolden, and Freeman (1946) described 26 cases treated by intrasphincteric resection following the technique of Pauchet, and made a plea for wider use of surgery, stressing the ineffectiveness and dangers of other methods of treatment. Breidenbach and Slattery (1948) described 18 cases treated by sacro-perineal excision of the stricture and primary anastomosis of bowel to anus.

The use of the broad-spectrum antibiotics in the treatment of the anorectal disease marked a great advance and many enthusiastic accounts of results of treatment have been published. Previous to this sulphonamides had been found fairly effective from 1941, but no success had been achieved with penicillin. Wright and Prigot (1951) described excellent results in 25 cases treated with aureomycin and considered that the drug was virucidal. Fletcher, Sigel, and Zintel (1951) treated 16 rectal cases with aureomycin and claimed definite and lasting improvement, but were more cautious in claiming virucidal properties. Rowe (1951) described his results using chloromycetin, and Banov (1953) described a small trial of aureomycin, chloromycetin, and terramycin, claiming equally good results with all three.

AETIOLOGY

The causative agent is a virus of the lymphogranuloma-psittacosis group which enters the body by venereal contact. Three varieties of the established disease are described: the inguinal acute lymphogranuloma venereum; the genital; and the anorectal chronic lymphogranuloma venereum.

The Inguinal Variety.—This occurs almost exclusively in the male, although the occasional case in the female is seen. A small ephemeral primary sore on the penis is followed at a varying interval by the appearance of the typical climatic buboes accompanied by mild constitutional symptoms (pyrexia, headache, and general malaise). The buboes may resolve or may suppurate.

The Genital Variety.—In the male this may follow the inguinal variety or may result from intra-urethral implantation of the virus. Lymph stasis,

urethral stricture, and periurethral abscess formation leads to gross elephantiasis and multiple fistula formation and destruction of tissues. In the female, primary inoculation of the virus on to the external genitals leads to œdema, ulceration, and destruction of these parts. It is usually found in conjunction with the anorectal variety and is then termed the genito-anorectal syndrome or esthiomene (Greek: eating).

The Anorectal Variety.—This form of the disease occurs predominantly in women and the mode of entry of the infection is much less well defined. No acute phase equivalent to that seen in the inguinal variety occurs, the first evidence of the disease being usually the passage of blood, mucus, and pus per rectum. It has been presumed that the virus enters by a primary sore situated on the vulva, vagina, or cervix and spreads backwards by lymphatic pathways to invade the rectum from without, although there is considerable evidence to prove that the infection is implanted directly on the anal mucous membrane. In the anorectal variety in the male, it is accepted that infection occurs by direct implantation, either through the practice of sodomy or probably from 'spill' at the time of intercourse conducted under very lax hygienic conditions.

A severe proctitis ensues spreading upwards to cause, in many cases, a proctosigmoiditis. After a variable time, from months to years, desquamation of the mucous membrane and fibrosis occurs, termed the 'prestricture phase' by Spiesman, Brotman, and Levy (1937), and finally stricturing supervenes.

The disease is largely confined to women; in our experience, all were of Negro extraction and usually of poor social status.

CLINICAL MANIFESTATIONS OF RECTAL DISEASE

The earliest symptom and most common manifestation of the disease is the proctitis or prestricture phase, the passage of blood pus, and mucus with spurious diarrhœa. Patients tolerate this for a surprisingly long time, thinking that they have piles, in view of the intermittent bleeding. Some seek advice only when early stricturing supervenes, complaining then of cramp-like abdominal pain, distension, constipation, and the passage of 'pencil' stools. A few cases are first seen in the stage of actual obstruction, although this is surprisingly rare. They may present with recurrent peri-anal abscesses or with multiple fistulæ-in-ano.

Rectovaginal fistulæ are common, occurring at the same constant site, the anorectal ring, and the passage of fæces per vaginam may be the first complaint. Others may present with the fully developed genito-anorectal syndrome.

The Rectal Lesions.—Three types may be seen, but in our experience it is not always easy to classify a particular case as the three may coexist, one feature predominating over the others. The types are: (1) proctitis only; (2) proctitis and stricture; (3) stricture only. It must be emphasized, however, that the definition of what constitutes a stricture is not clear cut. The mere gripping of the finger by the rigid walls of the rectum in the late stages of proctitis should not be classified as a stricture. The term should be used only for cases where there is definite obstruction to the passage of the finger or to an instrument.

Proctitis.—This probably represents the first manifestation of the disease in the majority of cases. In the florid stage a very intense reaction occurs resulting in the outpouring of pus in large quantities. It is a granular proctitis with a characteristic feel resembling morocco leather to the examining finger. In some cases larger polypoid granulations can be felt. On proctoscopy the appearances are those of fairly intense inflammation. The mucous membrane is engorged, bright red, and œdematous and dotted with punctuate hæmorrhages giving it a velvety appearance. Pus mingled with mucus pours down from above. Superficial ulceration and polypoid masses of heaped-up mucous membrane may be present. Histologically the changes are not remarkable, a fairly intense non-specific granulomatous inflammatory process being observed.

FIG. 207.—Tubular stricture involving rectum and lower part of pelvic colon.

The Stricture.—The stricture varies greatly in its density from a slight constriction gripping the finger to complete stenosis not admitting the smallest probe. The lowest point of the rectal stricture is at 3–5 cm. from the anal verge and below this the anal canal shows proctitis and thickening. The 'face' of the stricture is smooth and atrophic, and it can often be split open as the finger is inserted farther.

Barium enema studies which have been performed on the majority of patients in this series show that the stricture is usually long and tubular involving the whole rectum and often the lower part of the pelvic colon (*Fig.* 207). When a shorter length is involved the stricture appears conical (*Fig.* 208), and occasionally a very short length of bowel is involved, giving a diaphragmatic stricture (*Fig.* 209).

A minority of the cases present with a 'dry' stricture only (Type 3), there being no evidence of proctitis. In many of these, however, there is loss of mucous membrane and fibrosis throughout the rectal wall—evidence of previous 'burnt out' proctitis—and it is doubtful if stricture ever occurs without a preceding proctitis.

Lesions above the Rectum.—Little stress has been laid in the past on the fact that this disease affects not only the anus and rectum, but the left side of the colon also. Barium enema studies have

revealed that in most cases there is a sigmoiditis present as well and, in some, involvement of the colon up to the splenic flexure. The sigmoid colon shows a characteristic shortening of its total length. In the Negro the sigmoid colon is particularly long and pendulous, but as a result of the disease it becomes a short, thickened, inelastic loop (*Figs.* 210, 211). There may be localized areas of stricturing

FIG. 208.—The short conical stricture.

FIG. 210.—Stricture of rectum and pelvic colon showing pericolic sinuses and shortening of pelvic colon.

in the left side of the colon with apparently normal bowel between. The bowel in other cases may show an absence of haustration and a tubular appearance similar to that seen in ulcerative colitis.

DIAGNOSIS

The established case of rectal stricture is very obvious and it is doubtful if there is any other common cause of this condition. The presence of

FIG. 209.—The short diaphragmatic stricture. There are three short strictures in this case, one at the anal verge, a second in the rectosigmoid region, and a third in the descending colon.

FIG. 211.—Stricture of rectum with extreme narrowing and shortening of pelvic colon.

discharging sinuses, condylomata, and lymphœdema makes the diagnosis certain. At the stage of proctitis, however, the diagnosis is somewhat presumptive and is based on the clinical history, the

sigmoidoscopic appearances, and the radiological findings coupled with a positive Frei intradermal test or complement-fixation test.

The Frei Intradermal Test.—This test, introduced in 1925, is highly specific for the disease and its value has been proven irrefutably. It is, however, expensive, time-consuming for the patient, and does not lend itself to large-scale testing of suspects. We have not used the test routinely.

The Complement-fixation Test.—This test, more recently introduced in 1940, has been used almost exclusively in our series in an attempt to evaluate its usefulness. It has certain advantages over the Frei test, being more simply and rapidly performed and requiring only one attendance by the patient. It is probably more delicate, and gives some quantitative idea of the severity of the infection and, in the acute disease, of the efficacy of treatment. In the chronic cases, however, evaluation of the test is more difficult. Very high complement-fixation titres are obtained in cases showing no more severity of the disease than in those with low or even with negative titres. We have also found that the titres do not drop significantly *pari passu* with improvement or apparent cure of the disease, as can be seen in *Table I* which shows the titres obtained in 10 sample cases all classified as ' clinically cured ' two years or more after treatment.

Table I.—Asymptomatic Cases (Clinical Cure) at Two-year Follow-up. Complement-fixation Test Results

Case No.	*Highest Previous Dilution*	*Present Dilution*
1	1 : 10	Neg.
2	1 : 160	Neg.
3	1 : 640	1 : 40
4	1 : 160	1 : 40
5	1 : 1280	1 : 640
6	1 : 2560	1 : 1280
7	1 : 640	1 : 40
8	1 : 1920	1 : 1280
9	1 : 160	1 : 640
10	1 : 40	1 : 640

Cases 1 and 2 have been rendered sero-negative and these may be classed as complete cures. In *Cases* 9 and 10 the titre has actually increased slightly. In the remaining cases there has been a slight drop in the titres (1–3 dilutions).

TREATMENT

Our experience is based on a series of 91 cases seen at the University College of the West Indies from January, 1953, to March, 1956. Of these, 71 cases seen before January, 1955, have been followed up this year (1956) to assess the results of treatment a year or more after its completion. The incidence of the disease by sex and age and the type of disease are shown in *Table II*. All these patients were of Negro extraction.

This work was part of a large-scale project for the study of the lymphogranuloma-psittacosis group of viruses in Jamaica initiated by Dr. M. Sigel and Dr. C. F. Burgoon of the Children's Hospital, Philadelphia. The project involved the assessment of the efficacy of the broad-spectrum antibiotics in the treatment of the chronic types of lymphogranuloma and three antibiotics were tested in succession, chloromycetin (chloramphenicol), erythromycin, and aureomycin (chlortetracycline). All cases were admitted to hospital for antibiotic treatment, which was given whether subsequent surgery was indicated or not. Investigations included full blood examinations and serological testing, barium enema, sigmoidoscopy, and biopsy in many, though not in all cases. Sigmoidoscopy was also performed at regular intervals to follow the course of the disease during and after treatment.

Antibiotic Treatment.—The numbers treated with each drug are shown in *Table III*. Maximum dosage of each drug (2 g. daily for 14 days—total 28 g.) was given except to a few patients who either defaulted or who would not tolerate the drug. Side-effects were minimal (in 2 cases only was the drug stopped owing to the patients vomiting the capsules) and there were no serious complications. One case receiving chloromycetin had a leucopenia of 2000 white cells but this rapidly recovered and there was no proof that the drug was responsible. All the blood investigations were repeated at weekly intervals while the patient was in hospital.

Table II.—Sex and Age Incidence: Type of Disease (*Total No. of cases seen before January, 1955 = 71*)

Sex Incidence.—Female, 65. Male, 6.

Age Incidence	*Number*
10-19 years	1
20-29 ,,	13
30-39 ,,	17
40-49 ,,	24
50-60 ,,	15
Unknown	1

Clinical Type of Disease	*Female*	*Male*
Proctitis and stricture	49	4
Stricture only	10	1
Proctitis only	9	1
Other lesions (rectal involvement minimal)	3	0

Table III.—Antibiotic Assessment

Total treated with antibiotic plus or minus surgery		69
Chloromycetin	31	
Erythromycin	15	
Aureomycin	23	
Cases traced one year or more after treatment		50
Good results		44
Antibiotic alone	27	
Plus surgery	17	
Equivocal or poor		6
Antibiotic alone	3	
Plus surgery	3	

Thirty cases were treated by antibiotic alone; 26 of these (86 per cent) were assessed as ' clinical cure ', i.e., no symptoms, minimal or no evidence of disease, but complement-fixation test still positive.

Great subjective improvement was noted by the majority of patients immediately after the end of the treatment. The pain and tenesmus and the rectal discharge ceased and the patients' general condition improved strikingly. In some, however, the symptoms returned on withdrawal of the drug and for these cases a course of a different antibiotic was given with good results. No marked difference in the therapeutic effect of these three drugs was noted. There is no proof that these agents are virucidal in chronic cases, although in the acute inguinal type of disease they appear to be effective in completely eradicating the disease, as shown by disappearance of all clinical evidence of disease and by reversal of the complement-fixation test.

Antibiotic Assessment.—It was felt that follow-up should be performed at not less than a year from

the time of administration of the antibiotic in order to assess the permanence or otherwise of the result. This has been attempted on the first 71 cases of the series, all treated before January, 1955, but follow-up in this country of bad communications and on patients who, if well, are extremely reluctant to return to hospital, gives a poor percentage of patients traced.

It will be seen from *Table III* that 88 per cent have shown a good result from antibiotic treatment alone or combined with surgery. In many of the surgical cases the antibiotic was merely an ancillary, surgery being planned from the start, but in several cases with severe fibrous stricturing or with rectovaginal fistulæ there was such immediate improvement in signs and symptoms that surgery was postponed or avoided altogether. The effect of the drug must be mainly on the inflammatory component of the disease and not on the virus itself, and this explains the apparent 'widening' effect on actual stricturing, which in the early stages is inflammatory and œdematous, only later resolving into organized fibrous tissue.

At present the criteria for assessing cure of this disease are rather crude, depending mainly on the patients' subjective evaluation and on the evidence of the examining finger and the sigmoidoscope. The complement-fixation test has so far not given much help in assessing the effects of the antibiotics, although it is possible that titres may drop very slowly, and a longer period of observation is required. It seems reasonably established that the broad-spectrum antibiotics can arrest this disease at the proctitis and prestricture stage, virtually eliminating the incidence of stricture and esthiomene, while in the established stricture they are capable of producing marked subjective improvement.

SURGICAL TREATMENT

The indications for surgery are: the established stricture not admitting the finger, causing obstructive symptoms; multiple stricturing in the large bowel; an irreparably damaged anal canal; persistent rectovaginal fistulæ; severe esthiomene; and acute intestinal obstruction.

Palliative Methods.—Many palliative methods have been tried in the past, the most enduring one being prolonged intermittent dilatation. Most surgical clinics condemn its use on the grounds that it is ineffective in maintaining the lumen and that it can be dangerous, overstretching of the stricture leading to splitting and severe bleeding. In the Negro patient particularly, any attempt at dilatation of fibrous tissue produces a violent tissue-reaction with consequent great stimulus to proliferation. We have not employed rectal dilatation except in so far as regular rectal examination with the finger or sigmoidoscope does dilate the strictured area.

Colostomy.—Colostomy may have to be performed as an emergency measure for cases presenting with acute intestinal obstruction. A decision should be made if possible at the time of operation as to whether it is likely to be a permanent or temporary colostomy. If permanent, a left iliac colostomy is indicated, but if further surgery is likely, a transverse defunctioning colostomy is preferable, as the bowel may be affected by the disease above an iliac colostomy.

Every effort should be made not to leave permanent colostomies with the diseased rectum still in situ. We have seen the disease spread up to the colostomy stoma, while in most cases the discharge of blood and pus still continues, although in smaller quantities.

Resection of the Diseased Area.—

Abdominoperineal Resection.—This is performed where there is no possibility of restoring continuity owing to destruction of the sphincters, severe perirectal disease with rectovaginal fistulæ, or where there is disease involving the colon too extensively for any pull-through or anastomotic operation to be performed.

Perineal Resection after preliminary colostomy (Lockhart-Mummery, 1934) as advocated by Bacon (1941) has not been practised by us as there is some objection to leaving a small distal stump of pelvic colon which may harbour disease. It is also technically a difficult operation to perform on these patients without abdominal mobilization of the rectum, as previous pelvic inflammatory disease is so often found to have obliterated the normal anatomical planes.

Restorative Resection.—This is the most desirable form of treatment, as many of these patients are young and should not be condemned to permanent colostomy unless all other measures have failed. The indications for this type of operation have certainly increased with the preliminary use of antibiotics which minimizes the hazards of immediate sepsis and guards against recurrence. Before considering such an operation, careful radiological assessment of the bowel must be made and the integrity of the sphincters tested clinically. In those cases where the anus is surrounded by condylomata and completely replaced by fibrous tissue, no such operation should be considered. The most favourable cases are those with strictures 5 cm. or more from the anal margin, though some cases with radiological evidence of stricturing down to the level of the sphincters have been successfully resected, and continuity restored.

The Abdomino-anal 'Pull-through' Operation.—This type of operation has not been popular with British surgeons for two reasons: that it cannot be radical enough for cancer, and that it leaves the patient nothing more than a poorly controlled perineal colostomy owing to the complete loss of rectal sensation. However, for this inflammatory condition it has certain advantages over any anastomotic operation since no suturing in the rigid inflamed bowel is necessary. In our experience some return of 'rectal' sensation can be achieved, and control, though not always perfect, is adequate. Slight soiling and mucus discharge is more easily tolerated by the lower social stratum of patient in which this disease occurs than it would be by the upper strata.

Technique: We have followed with slight modifications the technique of Hartmann and Pauchet quoted by Wright and others (1946) of intrasphincteric resection. These workers perform a preliminary iliac colostomy and use this opportunity to assess the state of the left colon and to decide

whether a restorative operation will be possible. The second stage is a purely perineal excision and 'pull-through'. We feel that a transverse colostomy is preferable (*see above*), and the second stage consists of an abdominoperineal excision and 'pull-through'. This allows full inspection and mobilization of the left colon.

Procedure: The patient is positioned as for the synchronous combined abdominoperineal excision of the rectum. A left paramedian incision is made. The bowel is then inspected for evidence of inflammatory change. The affected bowel is shortened, puckered, and much thickened, the adjacent epicolic glands being enlarged, although glandular involvement is not marked. A decision has to be made as to how much bowel to resect; in most cases the distal part of the pelvic colon is involved. In others, involvement of the pelvic and iliac colon and occasionally of the ascending colon is found, and the splenic flexure then has to be mobilized for the pull-through. The bowel is mobilized and packed into the pelvis, but the peritoneum is not closed over it until the perineal part of the procedure is completed.

Table IV.—Cases subjected to Surgical Treatment

Total No. of Cases 20		
Colostomy	3	
Abdominoperineal resection	6	
Abdomino-anal pull-through	7	9
Abdominosacral	2	
Resection of pelvic stricture	1	
Internal proctotomy	1	

Perineal part: The anus is closed and a circular incision is made around the anal margin. The dissection is continued deeply, separating the sphincteric ring from the mucous membrane of the anal canal. This can be the most difficult part of the operation, and it may be impossible in those cases where the stricture has involved the anal musculature. A second incision is made across the perineum from one ischial tuberosity to the other, convex forwards, its most anterior part being immediately posterior to the vagina. When the dissection has been deepened down to the perineal body, a flap containing the sphincter muscles can be turned down and the rectum dissected out anteriorly and posteriorly until the peritoneum is reached and opened anteriorly. The bowel can now be pulled down (although considerable further mobilization may be required) through the anal musculature. The diseased portion is cut away and the pelvic colon sewn to the circular cut edge of the skin.

Many authors have stressed the difficulty of the operation due to the dense fibrosis in the perineal tissues, the perirectal inflammation, and the presence of sinuses. We have found, however, that it is only at the lower end at the anal margin that there is a real problem, the process at this point usually invading the vagina, often with a small rectovaginal fistula being present. The preservation of the intact sphincter ring is extremely important, and if it is found impossible to identify the muscle ring, the operation is best abandoned. In the more recent cases I have found it advisable not to suture the cut bowel to the anal margin as retraction is liable to occur with sloughing of the suture line and consequent fibrosis, but to leave the cut end of the bowel protruding with a crushing clamp applied which is allowed to fall off as the bowel end sloughs.

Table V.—Analysis of Abdomino-anal and Abdominosacral Operation Cases
(*Results 1 year or more after operation: 4 good, 2 satisfactory, 3 poor*)

Case	Sex	Age	Lesion	Operation	Result at Follow-up
R. J.	F.	34	Stricture 5 cm.	Abdomino-anal March, 1954	February, 1956:— No bowel symptoms. Continent. Rectal sensation. Mild neurogenic bladder
M. M.	F.	35	Severe stricture of rectum and pelvic colon	Abdomino-anal December, 1954	March, 1956:— Some recession of colon—post-operative stenosis. Internal proctotomy. Continues monthly dilatation
E. J.	F.	52	Stricture 5 cm. Rectovaginal fistula	Abdomino-anal July, 1954	March, 1956:— Stenosis at anal margin. Poor control. Monthly dilatation
I. G.	F.	40	Stricture 5 cm.	Abdomino-anal January, 1955	April, 1956:— Not full control but patient is well satisfied. No stenosis but sphincter tone poor
E. D.	F.	50	Stricture 5 cm. Rectovaginal fistula	Abdomino-anal May, 1955	May, 1956:— Stenosis—poor control. Vaginal fistula persists. Patient can manage
D. B.	F.	30	Stricture 5 cm.	Abdomino-anal February, 1955	May, 1956:— Good control. Small fistula at colostomy site
A. D.	F.	50	Stricture 3 cm. Rectovaginal fistula	Abdomino-anal October, 1954	February, 1956:— Good result. No bowel symptoms. Control satisfactory
L. P.	F.	31	Stricture 3 cm. Rectovaginal fistula	Abdominosacral October, 1954	March, 1956:— Excellent result. No symptoms. Full control—claims rectal sensation present
V. B.	F.	35	Stricture 5 cm. Rectovaginal fistula	Abdominosacral November, 1954	March, 1956:— Good result. Slight discharge from persisting sacral sinus. Full control

Other Operations.—Abdominosacral excision with anal anastomosis has been performed on 2 cases. This operation, if successful, gives a much superior functional result as the anal mucous membrane is preserved. In one of these cases, however, there has been a persistent fistula probably as a result of osteomyelitis of the sacrum.

Of 20 cases submitted to surgery up to January, 1955, 9 were treated by restorative resection

FIG. 212.—Specimen of abdominoperineal resection of rectal stricture showing condylomata at anal margin and a rectovaginal fistula.

FIG. 213.—Specimen removed by abdominoperineal resection showing extreme narrowing of lumen, thickening of the bowel wall, and replacement of mucous membrane by hæmorrhagic granulation tissue.

(*Table IV*) and the results a year or more after operation are shown in *Table V*.

The naked eye appearance of the diseased bowel is shown in *Figs.* 212, 213. Both specimens were obtained from abdominoperineal resections. *Fig.* 212 shows the extensive condyloma formation round the anus, and a rectovaginal fistula ; *Fig.* 213 shows the hæmorrhagic mucous membrane and the thickening of the submucosa.

The histological appearances are shown in *Fig.* 214. These are in no way specific, showing merely chronic and subacute inflammation. There is stripping of the mucosa and considerable thickening of the submucosa.

DISCUSSION

Several theories have been advanced for the pathogenesis of the rectal stricture though none can be said to be proved. The lymphatic theory of spread of the disease has been most widely held in the past to explain the formation of stricture in the female, whereas in the male it has been accepted that infection reaches the bowel by direct implantation as a result of sodomy.

Bensaude and Lambling (1936) contended that the disease, having entered through a primary sore situated " deeply vaginal ", passes to the perirectal tissues and spreads directly through the rectal wall to the mucosa, the stricture thus forming from without inwards, encircling the rectum and sparing the mucous membrane until the last. In support of this they quote the incidence of stricture without proctitis seen in their series of 80 female cases, 72 showing

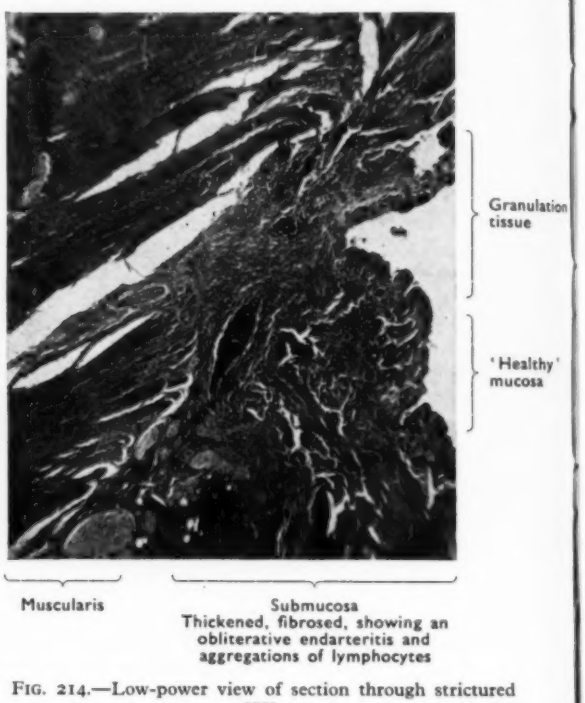


FIG. 214.—Low-power view of section through strictured area.

stricture alone. In their 148 male cases, however, 78 showed proctitis and stricture. They also state that 80 per cent of the male cases confessed to the practice of sodomy.

There are several points which militate against this theory. Firstly, there is no direct evidence of the existence of a primary sore situated deep in the vagina or on the cervix. Primary sores admittedly have been seen at the vaginal orifice and on the fourchette, and the very common appearance of rectovaginal scarring at this site and of actual rectovaginal fistula might lend support to the theory that the virus enters at this point. Lymphatic spread from here, however, would not be to the rectum, but to the inguinal or iliac glands. The comparatively infrequent cases of inguinal bubo in the female might be explained in this fashion. The theoretical primary sore high in the vagina or in the cervix should lead to some permanent enlargement of the pelvic glands akin to the residual enlargement of the inguinal glands in the male. But in the course of operations on these cases pelvic-gland enlargement has been conspicuous by its absence.

Secondly, the incidence of stricture with proctitis and stricture alone given by the above authors does not agree with figures quoted by other workers, or with our own. Grace (1941) found proctitis in 92 per cent of his female cases, and our experience

is similar to this. A stage of proctitis almost certainly precedes stricture formation in the majority of cases.

Thirdly, if the virus enters through the genital tract, why should it then show this elective affinity for the rectal tissues? No similar spread occurs in carcinoma of the genital tract. The lymphatic drainage of the upper third of the vagina is to the obturator and medial external iliac nodes. In his authoritative book on malignant disease of the genital tract, Way (1951) does not mention lymphatic spread to the rectum from carcinoma of the cervix or vagina.

Fourthly, the histological appearances of the stricture do not suggest an inflammatory process spreading from without, but rather a process most severe in the submucosa and decreasing in intensity in the outer coats of the rectum.

It might be conceded that in those cases of stricture alone with no evidence of previous proctitis (which in our experience are rare) the infection has reached the rectum from without, and in this connexion Ernest Miles's (1939) concept may be quoted of the rectal stricture arising as a result of infection from pelvic inflammatory disease spreading along the uterosacral ligaments and involving the rectum as the ligaments pass backwards on each side in close contiguity with it.

In the majority of cases the infection is acquired by direct implantation into the anal canal. This mode of infection is accepted as being probably the only one in males. It is known from experimental work on the chimpanzee that the virus can be easily implanted into the anorectal mucosa, and it seems reasonable to assume that this can happen in women as a result of natural intercourse under lax hygienic conditions. Grace (1941) after analysis of his 128 cases comes to the same conclusion.

It seems then that after implantation of the virus in the rectum an intense proctitis ensues and this stage may last an indefinite time from a few months to several years. This has been aptly called the "prestricture phase" (Spiesman, Levy, and Brotman, 1937). Eventually fibrosis follows the inflammatory infiltration, and stricturing commences. The process of fibrosis is greatly aggravated in the Negro (the so-called "fibroplastic diathesis" postulated by Rosser (1923)) and the stricture forms very readily.

The reaction of the bowel to this infection appears to be entirely non-specific and bears many resemblances to that seen in localized ulcerative colitis and in regional iliocolitis, and it is tempting to postulate that this disease produces a similar reaction. Lumb (1951) discussing the pathological lesions caused by various bowel diseases—ulcerative colitis, regional enterocolitis, and so-called ileocæcal tuberculosis, suggested that they represented a non-specific response of the bowel to certain stimuli and that possibly sensitization played a part in their production. He has coined the term "cicatrizing entero-colitis" for this disease process, and perhaps it is not unreasonable to add a fourth causative agent—lymphogranuloma venereum.

SUMMARY

1. Anorectal lymphogranuloma is a disease entity which may become more common in Great Britain as a result of the influx of West Indian immigrants.

2. A historical review of the disease is given and the literature dealing with its surgical aspects is briefly reviewed.

3. The clinical aspects of the disease, the radiological findings, and the complement-fixation test are described.

4. Ninety-one cases of anorectal lymphogranuloma have been seen at the University College Hospital of the West Indies. Seventy-one of these, followed up for a year or more, are reviewed to assess the efficacy of treatment by antibiotics and by surgery.

5. Antibiotic therapy produced good results in 88 per cent of cases.

6. The indications for surgery are described. The abdomino-anal 'pull-through' is a suitable operation when radical removal of the strictured area is indicated. A brief description of the operation is given.

7. The mode of entry of the virus is discussed and it is suggested that the bowel reacts to it in a non-specific manner, similar to the reaction seen in regional enterocolitis (Crohn's disease), or ulcerative colitis.

Acknowledgements.—My thanks are due to Professor G. H. C. Ovens, O.B.E., F.R.C.S., for permission to publish these cases, to my colleagues, Mr. C. C. Gardner and Mr. H. Annamunthodo, for allowing me access to their patients and case-records, and to our surgical registrars, Mr. J. B. Self and Mr. A. A. Belton, for their help in statistical work and follow-up.

The aureomycin was kindly donated by Messrs. Lederle Laboratories Ltd., who are providing continuing supplies of achromycin.

REFERENCES

BACON, H. E. (1941), *Sth. med. J., Nashville*, **34**, 31.
BANOV, L., jun. (1953), *Ibid.*, **46**, 269.
BATCHELOR, R. C. L., cited by HAWE, P. (1951).
BENSAUDE, R., and LAMBLING, A. (1936), *Proc. R. Soc. Med.*, **24**, 1441.
BREIDENBACH, L., and SLATTERY, L. R. (1948), *Ann. Surg.*, **128**, 1079.
DURAND, M., NICHOLAS, J., and FAVRE, M. (1913), *Bull. Soc. méd. Hôp., Paris*, **35**, 274.
FINDLAY, G. M. (1933), *Trans. R. Soc. Trop. Med. Hyg.*, **27**, 35.
FLETCHER, A., SIGEL, M. M., and ZINTEL, H. A. (1951), *Arch. Surg., Chicago*, **62**, 239.
FREI, W. (1925), *Klin. Wschr.*, **4**, 2148.
GRACE, A. W. (1941), *Bull. N.Y. Acad. Med.*, **17**, 627.
HARTMANN, H. (1922), *Lancet*, **1**, 307.
HAWE, P. (1951), *Proc. R. Soc. Med.*, **44**, 426.
HELLERSTROM, S., and WARSEN, E. (1930), *Proc. 8th int. Congr. Derm. Syph.*, 1147.
HUNTER, JOHN (1786), *Venereal Disease*, 265. London.
LEVADITI, C., RAVANT, P., and SCHOEN, R. (1932), *C.R. Soc. Biol., Paris*, **109**, 285.
LEWIS, R. I., cited by HAWE, P. (1951).
LOCKHART-MUMMERY, J. P. (1934), *Diseases of the Rectum and Colon*, 2nd ed., 326. London: Baillière.
LUMB, G. (1951), *Brit. J. Surg.*, **39**, 233.
MARTIN, C. F. (1933), *J. Amer. med. Ass.*, **101**, 1550.
MILES, E. (1939), *Rectal Surgery*. London: Cassell.
MORGAN, NAUNTON C. (1937), *Practitioner*, **89**, 421.
PRINGLE, J. S. M., cited by HAWE, P. (1951).

ROSSER, C. (1923), *Amer. J. Surg.*, **37**, 265.
ROWE, R. J. (1951), *Ibid.*, **81**, 42.
SIGEL, M. M. (1954), "Studies on the Psittacosis-Lymphogranuloma Venereum Group". Preliminary communication (not published).
SPIESMAN, M. G., LEVY, R. C., and BROTMAN, D. M. (1937), *Amer. J. dig. Dis.*, **3**, 931.
WAY, S. (1951), *Malignant Disease of the Female Genital Tract*. London: Churchill.
WOODS, F. M., and HANLON, C. R. (1944), *Ann. Surg.*, **120**, 598.
WRIGHT, L. T., BERG, B. N., BOLDEN, J. V., and FREEMAN, W. A. (1946), *Surg. Gynec. Obstet.*, **82**, 449.
— — and PRIGOT, A. (1951), *Ann. Surg.*, **133**, 364.

HÆMANGIOBLASTOMA OF BREAST

A REPORT OF THREE CASES

BY R. S. PATRICK, J. JARVIE, AND D. C. MILN

FROM THE UNIVERSITY DEPARTMENT OF PATHOLOGY, GLASGOW ROYAL INFIRMARY, AND THE SURGICAL WARDS, GLASGOW ROYAL INFIRMARY

MALIGNANT tumours of vascular origin attract attention because of their rarity and their distinctive clinical and pathological features. Consequently, there are many reports which usually describe a single case or a small group of cases. A significant number have presented as breast tumours, and this communication brings the total of these primary mammary cases in the literature to 18.

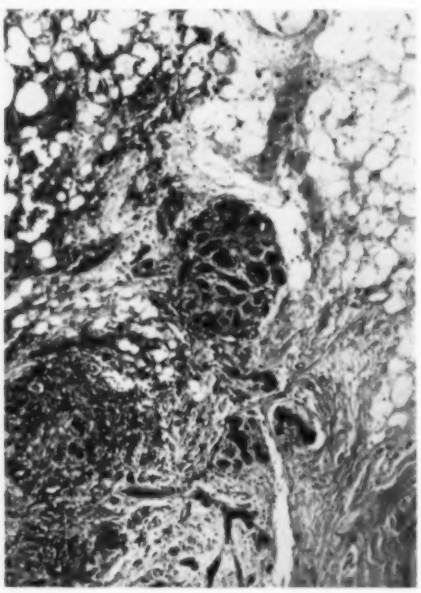


FIG. 215.—*Case* 1. Periphery of primary breast tumour. On the left there is infiltration of mammary connective tissue by deeply staining cells which form small vascular channels. There is no encapsulation. Hæmatoxylin and eosin. (× 40.)

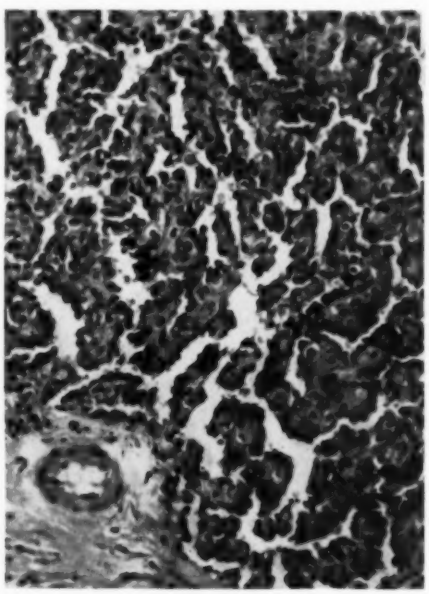


FIG. 216.—*Case* 1. A portion of the primary tumour showing numerous papillæ lined by prominent endothelial cells. The inner cells are spheroidal. Hæmatoxylin and eosin. (× 160.)

The lesion has been described under various names, such as hæmangio-endothelioma, angio-sarcoma, metastasizing angioma. We prefer the term hæmangioblastoma as the most appropriate title for a malignant tumour which consists of cells resembling primitive endothelium and having the capacity to produce blood vascular spaces.

CASE REPORTS

Case 1.—H. G. The patient, a woman aged 30 years, was admitted to Glasgow Royal Infirmary on June 23, 1947, two months after she had received a blow on the right breast. One week following this injury, when she experienced considerable pain, a swelling was noticed in the affected breast, but this did not alter in size until her admission.

On examination, the right breast was larger than the left due to a round firm swelling in the upper inner quadrant. The overlying skin was quite free from the tumour, but showed blue discoloration. The mass was not fixed to the underlying tissue and there were no palpable axillary glands.

A simple mastectomy, including resection of pectoral fascia and axillary contents, was carried out on June 27. Satisfactory healing was obtained and the patient left hospital on July 9.

Dissection of the specimen revealed a large hæmorrhagic tumour occupying much of the breast substance. Two small discrete nodules were seen at the periphery of the main mass. The overlying skin and the nipple showed no abnormality.

Hæmangiomatous dilatation of the blood-vessels was described in the original report, but the condition was regarded then as organization of a hæmatoma, this diagnosis being supported by the history of trauma. Recently, we have examined sections from several blocks taken from the original specimen and these all show much

freshly extravasated blood. Towards the periphery, however, cords of spindle-shaped cells appear to infiltrate the fatty tissue of the breast and the periglandular areolar tissue (*Fig.* 215). These cells resemble swollen endothelium, and in some areas they form the lining of narrow vascular channels. In addition, there are a few

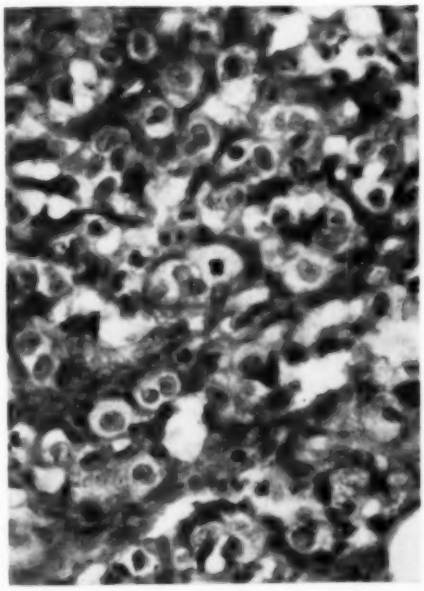


FIG. 217.—*Case* 1. Tissue from left axilla. A solid area consisting of spheroidal and spindle-shaped cells showing mitotic activity. Hæmatoxylin and eosin. (× 280.)

large vascular spaces into which project papillary processes, several cells thick. The inner cells of these papillæ are spheroidal and show nuclear hyperchromatism, pleomorphism, and some mitotic activity (*Fig.* 216). There is no distinct stroma other than the infiltrated connective tissue of the breast. There is no sign of encapsulation, but the angiomatous condition becomes sparse towards the periphery of the specimen and is absent, apparently, at the surface of resection.

Almost one year later the patient was re-admitted because examination of the left breast, which felt hot and heavy, had revealed two tumour nodules in its substance. Inferiorly, there was a mild degree of *peau d'orange*. In addition, several small soft masses, covered with blue skin, had developed in the lower portion of the right mastectomy wound scar.

A left simple mastectomy was performed on June 29, 1948. Several large venous channels were noted to run upwards along the lateral thoracic wall to the axilla. The recurrent nodules which had invaded the underlying pectoral muscle were excised from the right mastectomy scar.

Examination of the second breast after removal revealed two discrete masses, measuring 3 cm. and 1·5 cm. in diameter respectively. The microscopic features of these and of the small tumours in the earlier mastectomy scar are typical of hæmangioblastoma. Compared with the original specimen, hyperchromatism of tumour cell nuclei is more prominent, and a dense fibrous stroma separates many of the vascular spaces.

Early in July she complained of double vision and drooping of the left eyelid. Later, exophthalmos of the left eye developed, followed by blindness. During this period, when she was transferred to the Royal Beatson Memorial Hospital, Glasgow, dull red nodules appeared under the skin of the epigastrium and both axillæ, and in the upper lip. Portions of tissue from the lip and left axilla were submitted for histological examination in November. Unlike previous specimens, there are now extensive dense cellular areas having no stroma identifiable with hæmatoxylin and eosin, although staining of reticulin reveals an indefinite vascular pattern. The majority of tumour cells are spheroidal, with large nuclei and clear cytoplasm, occasionally vacuolated. Mitotic figures are

FIG. 218.—*Case* 1. Another portion of tumour from left axilla having the structure of a benign cavernous hæmangioma. Hæmatoxylin and eosin. (× 80.)

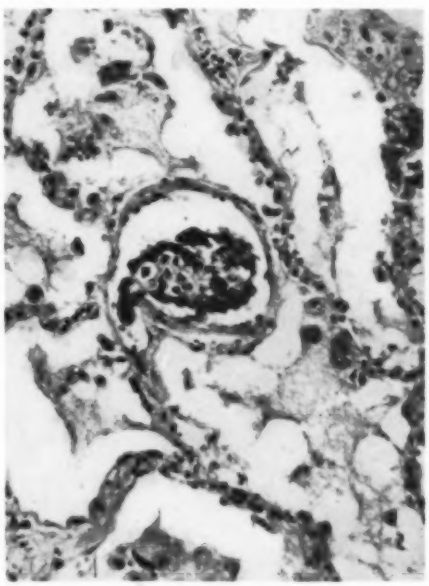


FIG. 219.—*Case* 1. A small tumour embolus within a pulmonary vessel. Hæmatoxylin and eosin. (× 160.)

numerous (*Fig.* 217). However, in some parts of these lesions, the appearance is indistinguishable from that of a benign angiomatous malformation (*Fig.* 218).

Deep X-ray therapy was given, but the patient died in a cachectic state on January 7, 1949.

At autopsy, the presence of angiomatous tumours was confirmed in the anterior abdominal wall, both axillæ, and left orbit. Numerous small tumours were seen under the visceral pleura bilaterally, and several tiny specimens

could just be detected macroscopically within each lung. The liver also contained many small foci of a uniform light brown colour, each surrounded by a zone of darker tissue, which proved microscopically to be hæmangioblastomata. Two small hæmorrhagic nodules were found in the wall of ileum, close to its mesenteric attachment, and the largest deposit was present in the right ovary, which weighed 100 g. and measured 6 cm. in its widest diameter. On section, this mass had a grey fleshy appearance with many small cysts containing either deep red blood-clot or yellowish-grey fluid.

There were no other findings of note apart from fatty change of myocardium, liver, and kidneys, and atrophy of the posterior lobe of the pituitary. There were neither macroscopic nor microscopic signs of neoplasm in the kidneys, adrenals, pituitary, and spleen, or in bronchial and para-aortic lymph-nodes.

Histological examination of these tumour deposits reveals features essentially similar to those of the biopsy specimens already described. Variation in structure between different parts of the same tumour, and in the lungs, between one small tumour deposit and another, is a notable feature. Tiny collections of tumour cells are found within pulmonary vessels at a distance from established tumour masses (*Fig.* 219) and, in one section, there appears to be well-differentiated tumour growth from the region of a small blood-vessel. In the liver small deposits are found in the portal canals, suggestive of vascular permeation.

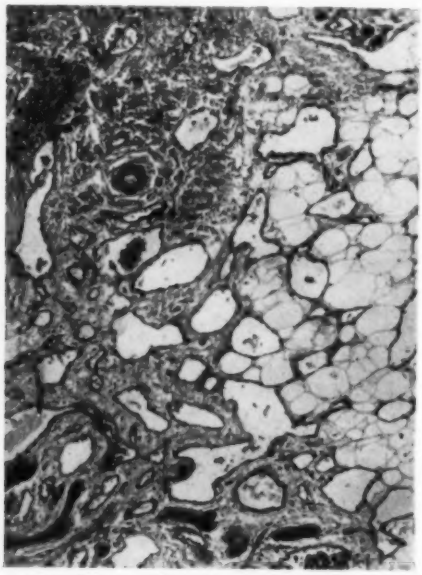


FIG. 220.—*Case* 2. Primary mastectomy specimen. Many dilated vascular channels are infiltrating the fibrous and adipose tissue of the breast. Hæmatoxylin and eosin. (× 48.)

FIG. 221.—*Case* 2. The tumour in the right pectoral region at the time of autopsy.

FIG. 222.—*Case* 2. A sagittal section has been made through the sternum. The mid-portion of the bone is invaded by tumour.

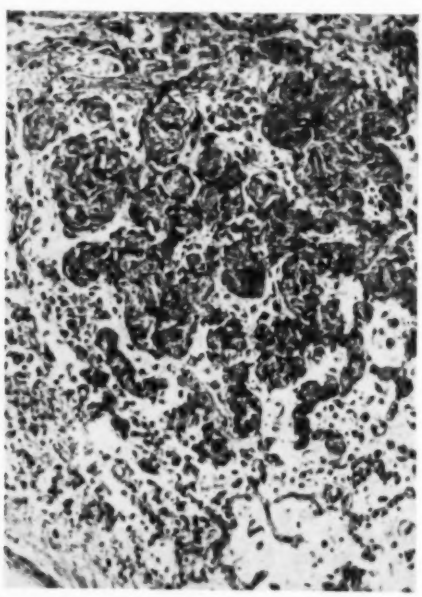


FIG. 223.—*Case* 2. Right lung. A small cluster of well-formed capillaries found on routine histological examination. Hæmatoxylin and eosin. (× 96.)

Case 2.—M. R. From June, 1948, until June, 1950, this patient, a woman aged 23, underwent treatment in hospital for pulmonary tuberculosis. On leaving the sanatorium, she immediately reported to the Out-patient Department of Glasgow Royal Infirmary because of a painless swelling in the right breast which had been present for fifteen months. In view of her history, tuberculous mastitis was considered and a course of streptomycin and P.A.S. was given. At first there appeared to be regression of the tumour, but enlargement occurred later. The mass,

indefinite in its outline, was 3 in. in diameter, with no apparent attachment to superficial or deep structures, but with blue discoloration of the overlying skin. There was no tenderness and no axillary glandular enlargement.

Simple mastectomy was performed on September 30, 1950. Dissection of the specimen revealed a hæmorrhagic tumour, not unlike placental tissue, and measuring 8 cm. in diameter, in the substance of the breast. Excision seemed adequate.

Histologically, the tumour consists of capillary and cavernous spaces lined by flat cells with spindle-shaped nuclei. Some of these spaces contain blood and there is evidence of extensive interstitial bleeding. The angiomatous vessels are situated between distorted and atrophic mammary acini and also within adipose tissue (*Fig.* 220); at the periphery of the specimen only the peri-acinar connective tissue is involved. In some areas the lining cells have large hyperchromatic nuclei and form papillary processes which extend into cavernous spaces. Spheroidal cells with large round nuclei and clear cytoplasm are seen in the centre of many of these papillæ. There are a few solid areas, formed apparently by heaping up of tumour cells, some of which show mitotic activity. The condition was reported as malignant hæmangioblastoma.

Within a few months there was recurrence in the region of the mastectomy wound in the form of two dark red nodules, each 2–3 cm. in diameter. These were excised together with pectoral muscle and axillary contents and the operation completed as in a radical mastectomy. Radiotherapy was given as soon as healing was complete.

The structure of each nodule is similar to the papilliform and solid areas of the primary tumour and there is extensive necrosis and hæmorrhage. Some solid areas with complete lack of canalization show much mitotic activity.

The tumour recurred in the right pectoral region and exploration on May 21, 1951, showed that it had penetrated deep to the thoracic cage and appeared to involve the mediastinal glands. Complete removal was impossible and profuse hæmorrhage was produced. There was repeated bleeding from the lesion until death occurred on July 24.

Autopsy was performed 12 hours after death. The morbid anatomical features could be classified as follows:—A large vascular tumour in the right pectoral region; multiple small angiomatous tumours in lung, liver, and kidney; and chronic pulmonary tuberculosis.

The Primary Tumour.—The skin and subcutaneous tissues of the right pectoral region, the site of mastectomy, were replaced by a large, dark red, nodular tumour which was roughly triangular in shape, the apex being in the axilla and the base extending from the second to fifth right costal cartilages (*Fig.* 221). Medial to this ulcerated area and overlying the body of sternum was a smooth subcutaneous swelling 10 cm. × 6 cm. Two small tumour nodules were present in a healed biopsy scar which passed downwards and medially from the main tumour mass.

Dissection of the anterior chest wall revealed direct invasion of the sternal body by the primary neoplasm (*Fig.* 222), but the inner periosteal surface was intact. Tumour extended through the third right intercostal space, where there was a small breach in the parietal pleura.

In the right axilla the tumour lay upon, but did not invade the muscles of the posterior axillary wall; nor was there invasion of blood-vessels, and the right upper limb was not œdematous. The lymph-nodes in this region had been removed previously.

Histologically, the tumour is a hæmangioblastoma consisting of vascular spaces of variable size lined with plump endothelial cells. Hæmorrhage, necrosis, and polymorphonuclear leucocytic invasion are extensive. The endothelial cells are pleomorphic, but mitotic figures are scanty. There are a few compact cellular areas where canalization is absent or imperfect, but the vascular nature of the tumour is apparent in all sections examined.

Visceral Tumour Deposits.—The lower lobe of right lung contained two spherical nodules, each about 1 cm. in diameter, which on section presented a hæmorrhagic appearance. Four nodules of similar morphology were found within the right lobe of the liver and a single tiny nodule could be seen in the medulla of the right kidney.

FIG. 224.—*Case* 3. The appearance of the breast at the time of the patient's first admission to hospital.

The microscopic features of all these tumours are identical with those of the primary growth. In addition, sections taken from various parts of both lungs to study the extent of tuberculous disease reveal several small capillary angiomatous tumours. These are small vascular spaces well filled with blood and lined by flat endothelium, typical of benign capillary hæmangiomata (*Fig.* 223). Unlike the first case, transitional forms and metastases within pulmonary vessels are not discovered.

Chronic Pulmonary Tuberculosis.—Extensive tuberculous disease was present and was clearly an important contributory factor in the death of the patient. A caseous area, 4 cm. in diameter, was found at the left apex and small foci of fibrocaseous disease were scattered throughout the remainder of this lung and in the right upper and lower lobes. Two pints of thin purulent exudate with scanty tubercle bacilli were present in the left pleural cavity.

Tuberculosis was confined to the thorax. There was no other abnormality of note apart from small foci of hepatic necrosis.

Case 3.—M. K. This young woman, aged 18 years, was admitted to Glasgow Royal Infirmary on October 23, 1954. For two months she had felt run down and listless. She had a swelling in her right breast of six months' duration, while shooting pains had been present in this region for three months. There had been a few blisters on the overlying skin which showed bluish-purple discoloration.

On examination, the right breast was almost the size of a melon and was dripping blood (*Fig.* 224); in fact, it was the presence of blood seeping through her clothing which caused her workmates to insist on her coming to hospital. The whole breast was rubbery firm with moderate pulsation, and a hæmic bruit was audible. Tenderness was slight. Hæmoglobin measured 32 per cent. Radiographic examination of the chest was negative.

After preliminary transfusion a simple mastectomy was performed on October 29, leaving a raw area 8 in. × 5 in. which was covered by a Thiersch skin-graft from her

right thigh. There did not appear to be invasion of pectoral muscle.

The operation specimen showed numerous plum-coloured areas, some bullous in character and measuring up to 1 cm. in diameter, in the skin, especially around the nipple. Section of the specimen revealed friable hæmorrhagic tumour, but no normal breast tissue.

Microscopically, the tumour consists partly of blood-filled spaces of irregular size and shape and lined by

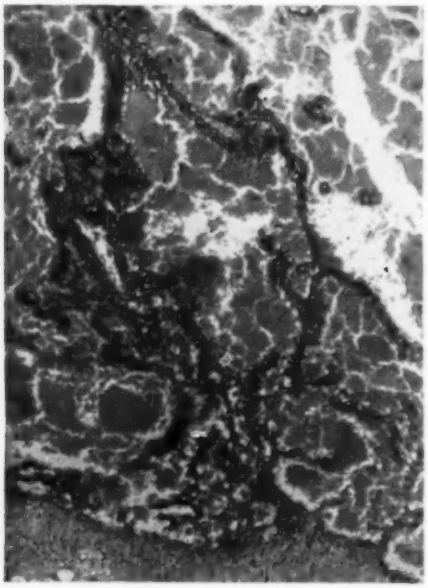


FIG. 225.—*Case* 3. Primary breast tumour. An area showing wide cavernous spaces filled with blood and separated by a thin stroma lined by flattened or spheroidal cells. Hæmatoxylin and eosin. (× 48.)

prominent spindle-shaped cells; such areas are typical of cavernous hæmangioma (*Fig.* 225). Elsewhere, the tumour is more cellular, and appears as solid masses of elongated cells or shows a cribriform or papilliform pattern. Cellular pleomorphism and nuclear hyperchromatism are not prominent but, in the solid areas especially, mitotic figures are seen, about one in each high-power field. A stroma of dense fibrous connective tissue forms an irregular network between collections of tumour cells. A few epithelial-lined structures, presumably remnants of mammary ducts, are seen in this stroma, but there is scarcely any adipose tissue (*Fig.* 226). There is extensive interstitial hæmorrhage and scanty leucocytic infiltration. Intra-epidermal bullæ containing serous fluid and blood are present.

Most of the skin-graft took well and on November 23 her hæmoglobin had risen to 75 per cent. A course of X-ray therapy was then started. While still attending for treatment, small nodules appeared around the margin of the skin-graft. These were removed on December 14 and were found on histological examination to be hæmangioblastomata with features identical with those of the primary tumour. Shortly thereafter she developed a cough and radiographic examination of her chest demonstrated pulmonary metastases. She died at home one month later and autopsy was not performed.

DISCUSSION

Although a relatively small number of cases of hæmangioblastoma of the breast have been described, a readily recognizable clinical picture has emerged. Our 3 patients have followed the classical pattern in that they were young women; all had breast swellings which had grown appreciably within a few months; the skin overlying the swelling was not attached to it, but was bluish in colour; no involvement of axillary nodes was apparent; and mastectomy, with or without radiotherapy, did not prevent early widespread metastases leading to a rapidly fatal issue, in our cases after an average of twenty months, the shortest being ten months. The initial appearance of these patients does not prepare the clinician for

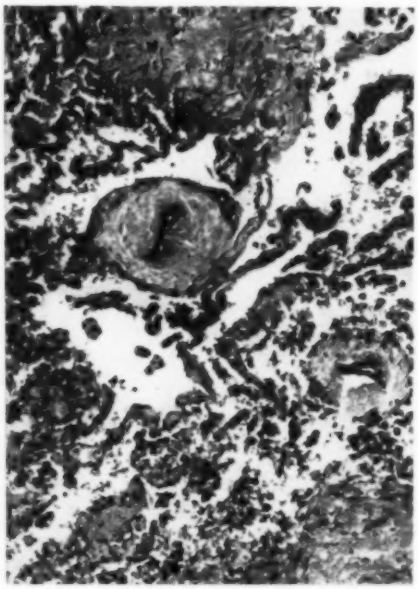


FIG. 226.—*Case* 3. A primary breast tumour showing an indefinite papillary structure. There are two atrophic mammary ducts surrounded by dense fibrous tissue. Hæmatoxylin and eosin. (× 80.)

the fulminating outcome, as the condition appears localized and the histological features may not be regarded as those of a highly malignant neoplasm.

In each case, the primary growth was a large friable hæmorrhagic mass with a microscopic structure which varies considerably from one part of the specimen to another. Thus, some areas have the appearance of benign capillary or cavernous hæmangioma, while others consist of solid masses of spindle-shaped or spheroidal cells with hyperchromatic nuclei and variable, but often marked, mitotic activity. Again, the structure of some parts lies between these extremes, such as the formation within vascular spaces of papillæ lined by hyperplastic endothelium. There is no evidence of encapsulation; on the contrary, especially in *Case* 2, invasion of adipose and areolar tissue by the more highly differentiated parts of the tumour produces a striking histological appearance. As Stout (1943) has observed, the vascular nature of the neoplasm preserves much of the invaded tissue which might otherwise undergo degeneration or necrosis. The structure of the recurring tumour nodules and of the metastases usually resembles that of the primary growth.

Similar clinical and pathological features have been noted in many of the cases previously described. The most recent account, including a review of all other reported cases, is that of McClanachan and Hogg (1954). These authors have described 3 new cases and re-examined 3 others investigated previously

by Adair and Herrmann (1946). All six were young women in the second or third decade, and in all the disease terminated fatally within a few years. Widespread metastases were found in those which came to autopsy. While the condition is common in young women, 2 of Stout's 3 cases were elderly subjects. The tumour may appear to be promoted by pregnancy (Enticknap, 1946), but this factor did not apply to our cases.

The patient described by Robinson and Castleman (1936), a girl aged 18, had a large vascular mammary tumour with the histological features of benign hæmangioma. However, local recurrence followed removal of this tumour, and deposits composed of cells with undoubted malignant characteristics appeared later at other sites. In our cases it is conceivable that a mistaken diagnosis of benign hæmangioma would arise only if examination had been confined to one or two small blocks taken from the primary tumour. On the other hand, it is difficult to be certain of the nature of the highly differentiated angiomatous structures found in the lungs of our cases in which post-mortem examination was carried out. It is necessary to consider whether hæmangioblastoma does produce metastases or whether these tumours which appear to be metastases are really the result of malignant change in multifocal angiomatous malformations. The following points seem to contradict the latter hypothesis :—

1. The disease runs a definite course, beginning in the breast and appearing later in other parts of the body. As Robinson and Castleman have observed, malignant change in multifocal sites would be expected to occur at one period of time.

2. Transitional forms between apparently benign and obviously malignant tumour were found in the lungs of our first patient.

3. In *Case* 1, tumour cells were seen within pulmonary vessels. Tibbs (1953) has illustrated a similar phenomenon in his case, a woman aged 37, in whom tumour growth may have been aggravated by pregnancy.

Apart from difficulty in the assessment of malignancy in an angiomatous growth, the condition must be differentiated from other hæmorrhagic and vascular neoplasms. Metastases from tumours such as renal carcinoma and chorionepithelioma might be mistaken for hæmangioblastoma, but these can be excluded with confidence in our 2 cases which came to autopsy. Careful histological examination is sufficient to exclude hæmorrhagic mammary cancer ; in this respect it is of interest to note the absence of axillary lymph-node metastases in *Cases* 2 and 3, while histological examination of the axillary masses in *Case* 1 reveals no trace of lymphoid tissue.

As noted in our first patient, when there is a history of trauma, the tumour may be mistaken for organization of a hæmatoma by vascular granulation tissue. Trauma was noted in 3 of McClanachan and Hogg's cases and in 1 of Stout's 3 patients. Stout considers that the infiltrative growth of capillaries in granulation tissue is similar to that manifested by the vessels in these malignant vascular tumours. In our experience, there is widespread infiltration of otherwise normal structures by small blood-vessels without accompanying fibroblasts, and this is not typical of a reparative process.

Finally, the tumour has to be differentiated from vascular neoplasms of connective tissue origin, especially Kaposi's sarcoma. This has been reviewed by McCarthy and Pack (1950) from their experience of 36 cases of Kaposi's tumour and 20 cases of hæmangio-endothelioma arising in various sites. The former usually presents as multiple nodules in the soft tissue of the limbs. These nodules tend to coalesce and metastases may appear in various sites, including lymph-nodes. Histologically, they bear a close resemblance to granulation tissue. The condition is usually found in males over the age of 40 and mammary cases are not described.

Hæmangioblastoma of the breast is, fortunately, a rare condition. Our 3 patients were seen within a period of 10 years during which 1376 cases of malignant breast tumour were examined. Mastectomy gives no apparent relief, but unfortunately the operation has only been undertaken when symptoms have been present for several months. In spite of the rarity of this tumour, therefore, we feel it is important to draw attention once more to its existence, in view of its predilection for young subjects, and the possibility of confusion with a relatively benign condition, exemplified in our cases by hæmatoma and tuberculosis of the breast.

SUMMARY

Three cases are described of hæmangioblastoma, a malignant tumour of vascular origin. Each arose in the breast, recurred locally after mastectomy, and finally produced distant metastases.

The condition is rare, but is of importance because of its tendency to occur in young subjects, its bad prognosis, and the difficulty of diagnosis in the early stages of the disease.

We are indebted to Mr. J. Dunbar and Mr. G. T. Mowat for permission to publish the clinical details of these patients. Dr. P. R. Peacock, of the Royal Beatson Memorial Hospital, has given us access to the post-mortem record of the first case together with many specimens of tissues preserved for histological examination. The photomicrographs were prepared by Mr. P. J. Elliott and the coloured photograph by Mr. W. Towler. Part of the cost of illustration was borne by the Carnegie Trust for the Universities of Scotland.

REFERENCES

ADAIR, F. E., and HERRMANN, J. B. (1946), *Surgery*, **19**, 55.

ENTICKNAP, J. B. (1946), *Brit. med. J.*, **2**, 51.

MCCARTHY, W. D., and PACK, G. T. (1950), *Surg. Gynec. Obstet.*, **91**, 465.

MCCLANACHAN, B. J., and HOGG, L., jun. (1954), *Cancer*, **7**, 586.

ROBINSON, J. M., and CASTLEMAN, B. (1936), *Ann. Surg.*, **104**, 453.

STOUT, A. P. (1943), *Ibid.*, **118**, 445.

TIBBS, D. (1953), *Brit. J. Surg.*, **40**, 465.

EXPERIMENTAL SURGERY

A COMPARISON OF SIX PROCEDURES DESIGNED TO INCREASE THE BLOOD-SUPPLY OF THE MYOCARDIUM

By E. R. DUCHESNE, O. A. ABBOTT, A. E. ROBERTS, and F. P. SALOMONE

FROM THE DIVISION OF THORACIC SURGERY, DEPARTMENT OF SURGERY, EMORY UNIVERSITY SCHOOL OF MEDICINE, GEORGIA

In the last twenty years the problem of coronary heart disease has become increasingly prominent, owing mainly to the regrettable fact that during this period a greater proportion of the persons affected have been active males under the age of 40, with the result that they have had their working potential restricted at a time in their lives when they would normally be expected to give of their best.

In several centres throughout the world the problems of this disease have been studied from many angles, and very little success has been achieved. One of the approaches has been surgical, and it is this that we propose to discuss in our short article. We desire to give an account of our own limited experience with certain surgical procedures carried out in our research department, and hope that the evidence presented will be thought of some significance, even though the series is a small one. Several authors have described their attempts to increase the blood-supply of the myocardium by applying some form of extrinsic collateral circulation. The principal end sought by all the surgical approaches is the same, but the method in each procedure is different.

In Great Britain the investigator who was prominent in the field was O'Shaughnessy, unfortunately killed in France in 1940. The method which he used was that of transdiaphragmatic omentopexy to the myocardium of the left ventricle, and the experimental animal used was the dog.

The American protagonist of the surgical approach was Claud Beck, of Cleveland, and it was after a visit to his department that we decided to try to reproduce some of the procedures that have been used by different individuals, and to see if there appeared to be any value in the surgical approach in independent hands, and, if so, which procedure gave the best all-round results.

The experimental animal which we used was the dog.

When studying a disease process in such an animal, it is desirable to reproduce the disease in the animal first, and then to attempt measures which will remove the disease process. In the case of coronary heart disease this is most difficult to do, and it was therefore necessary to apply an artificial principle.

The various procedures were performed on the animal first, and a period of time was allowed to elapse. An injury was then applied to the heart and the effect of the injury observed. The nature of this injury was such that if it were applied to an unprotected heart, it would cause enough damage to ensure that the heart would cease to beat effectively in a short period of time.

In this problem, the reversal of normal order—of treatment before disease—may not be to the disadvantage of the eventual result of the experiment, for it is believed that an ischæmic myocardium will develop a collateral more readily than a normal one, and therefore it may be argued that a procedure which will work on a normal myocardium will work even better in the presence of existing ischæmia. This point is of particular importance in the experimental work carried out by Vineberg, of Montreal, whose procedure will be described later.

Beck and Leighninger (1955) have pointed out that there are two methods by which the heart may fail after infarction in the experimental animals which they have investigated :—

1. The myocardium may have repeated infarctions or prolonged ischæmia due to sclerosis over a period of time, and survive. Gradually, however, muscle will degenerate or be replaced by such a quantity of fibrous tissue that it will make it incapable of carrying its work-load. This process may be termed ' muscle failure '.

2. In the other fashion, a localized portion of myocardium, the volume of which may be quite small, is subjected to infarction and becomes hypo-oxygenated in comparison with surrounding muscle. The difference in degree of oxygenation produces an area of differential electrical potential between two masses of muscle. The greater the difference in oxygenation between these two masses of muscle, the greater becomes the potential difference between them. This potential difference creates an electrically unstable heart, and the area of infarction

becomes an ectopic focus of contraction. Claud Beck termed this area a " trigger area ", for it can produce ventricular arrhythmias which can, and often do, result in ventricular fibrillation. This fatal arrhythmia is particularly prone to occur when there are two or more irritable foci, such as may result from repeated episodes of infarction.

When the heart ceases to beat effectively as a result of this electrical instability, the term ' mechanism failure ' has been used. In ' muscle failure ', surgical treatment is of no avail, because fibrous tissue cannot be metamorphosed to muscle. Attention was thus directed to ' mechanism failure ' in the hope that something might be discovered which would offer aid to the patient who had experienced coronary thrombosis. It was felt that if the electrical potential difference between the ischæmic area and normal muscle could be kept as low as possible, the immediate chances of electrically elicited arrhythmia would be reduced sufficiently to allow the heart to function adequately under low load, until such a time as it had regained stability and had developed its maximum collateral circulation. One way by which this difference may be decreased is to supply the anoxic area with more arterial blood than it would normally receive, and it is to this end that these various procedures have been developed. Beck and Leighninger (1955) have performed their operations on a large series of experimental animals, and have shown by very skilful application of the Mauz-Gregg backflow principle that the supply of a very small extra quantity of blood per minute to the injured area of myocardium will protect the heart from fatal arrhythmia during the critical state of infarction.

In our own experiments any such intricate test was impossible, for we were not in a position to do it at the time. We elected one test which would produce a major infarction and death in a significant number of instances. The test was the ligation of the anterior descending branch of the left coronary artery, immediately below its first septal branch. This manœuvre resulted in death by ventricular fibrillation as seen visually or on the electrocardiograph, in a maximum period of 3 hours, or a minimum of 12 minutes. Death occurred in 10 out of 12 of our control animals. The next step was to select a random series of mongrel dogs and to perform the various procedures. After a period of 4–12 weeks the animals were re-operated on and the anterior descending coronary artery was doubly tied, exactly as in the control group, and the mortality noted.

The survivors were allowed to live for 3 months unless taken by intercurrent disease, such as distemper or hepatitis, which are very common in this area. At the end of the 3-month period the animals were sacrificed, and examined for integrity of the double ligature and the presence of infarction.

The procedures which we used are described below, and short summaries of our results are given. It appears that even in the hands of a group which has had limited experience with the procedures, operative manipulation of the heart reduces significantly the immediate mortality of major infarction.

We have been asked on several occasions if we believe that vessels actually grow into the myocardium after these procedures, and in anticipation of this question we will give our opinion on the mechanism by which these procedures ' save ' the heart.

Probably the major element in all but Vineberg's operation is the dilatation of the capillary and intramyocardial blood-bed. This allows existing vessels to act as collaterals to an area deprived of its direct blood-supply. This is achieved in the Beck II procedure by aortic arterial pressure, and in the Beck I and Fauteux (1946) procedures by coronary sinus or great cardiac vein constriction. The same end is achieved, but less effectively, in Thompson's (1954) procedure, and in routine pericardial exploration, by the formation and contraction of fibrous tissue around the superficial veins.

The second factor is the growth of small vessels directly from the organ of collateral into the muscle of the heart wall itself. In two instances we observed these vessels under the microscope (in the Beck I procedure). In the case of Vineberg's internal mammary transplant, the collaterals derived are quite large and may easily be injected with plastic via that artery, and seen with the naked eye (Vineberg and Buller, 1955).

The third factor is the removal of the nerve-plexus around the base of the coronary trunk and aorta. This helps to prevent the development of reflex spasm in the rest of the coronary tree after obstruction of a vessel. This factor was stressed by Fauteux, and may also be seen by the naked eye. The plexus denervation in human patients has a further important function. Most patients upon whom procedures are performed without denervation receive no symptomatic improvement until collateral has developed. In the immediate post-operative period they are restless, apprehensive, and uncomfortable and are consequently subject to the physical and psychic dangers of anginal attacks, while those who have denervation performed are subjectively more comfortable immediately after surgery.

PROCEDURES

Unprotected Ligation.—Twelve operations were performed; 2 animals survived; infarction was present in 11.

Beck I.—The operation consists of thoracotomy through the fourth or fifth left intercostal space according to the point of maximum impulse. The lung is retracted posteriorly and maintained in position with packs stabilized by retraction sutures inserted longitudinally in the pericardium.

The pericardium is incised transversely just below the auriculoventricular groove, and the incision extends from the phrenic nerve as far back as the inferior pulmonary vein. With the aid of a wet sponge the heart is elevated by lifting the apex with the left hand. The termination of the coronary sinus is then easily seen where it enters the right auricle.

The epicardium is incised longitudinally over the coronary sinus, which is then separated from the circumflex branch of the left coronary artery, with a ball-point dissector (*Fig.* 227). A suture of No. 1 black silk on an atraumatic needle is then passed around the sinus from below, but not tied.

The parietal pericardium is then abraded with the Beck burr (*Fig.* 228) and then the ventricular

epicardium is similarly treated, care being taken to avoid main branches of the coronary arteries. If localized bleeding is excessive owing to an error in technique, gentle pressure with a dry sponge for five minutes will usually stop it. If that should fail, a piece of free pericardium may be stitched over the bleeding-point with shallow interrupted sutures of

FIG. 227.—Instruments used in operative procedures. A, Dissector; B, Pott's-type bulldog clamp; C, Beck clamp; D, Ball-point dissector; E, The Beck burr.

00000 atraumatic black silk. It must be emphasized, however, that free generalized oozing is essential.

When the abrasion is completed, a 3-mm. probe is laid alongside the coronary sinus and the previously placed suture is tied down over the probe to reduce the effective lumen of the coronary sinus to 3 mm. Powdered asbestos 0·2 g. is then spread over the heart and into the pericardium (Leighninger, 1955), and the incision in the pericardium is tightly closed with interrupted sutures of 000 black silk.

The chest is closed in the usual fashion.

Results.—We have performed this operation upon 16 dogs. Operative mortality was 1. The animal died at the insertion of the last skin suture, and at autopsy was found to have hepatitis. The other 3 dogs succumbed to intercurrent disease at the common pound. Twelve dogs were ligated. Eight dogs survived. The infarcts in the 4 deaths were all less than 1 cm. × 1 cm. on the anterior surface of the ventricle.

Fauteux.—The object of this procedure is to remove the vasoconstrictor nerves to the main coronary arteries, and to tie the great cardiac vein.

A left thoracotomy is performed through the third or fourth intercostal space. The lung is retracted posteriorly and stabilized with retraction sutures. The phrenic nerve is mobilized from the pericardium and gently retracted anteriorly. A longitudinal incision is made in the pericardium posterior to the phrenic nerve which extends from the pericardial reflection on the ascending aorta to a point about half-way between the auriculoventricular groove and the apex of the heart. The pericardial margins are then widely retracted and held in place by retraction sutures.

The ascending aorta and main pulmonary artery are then in plain view. There is a pad of fat lying in the aorticopulmonary artery groove, and this is grasped with forceps and gently dissected away. Beneath the fat pad, in an anterior and inferior direction, lies the origin of the left coronary artery. The connective tissue around the ascending and underside of the arch of the aorta is dissected off, and the area of origin of the left coronary artery displayed. The groove between the main pulmonary artery and the aorta is carefully developed superiorly

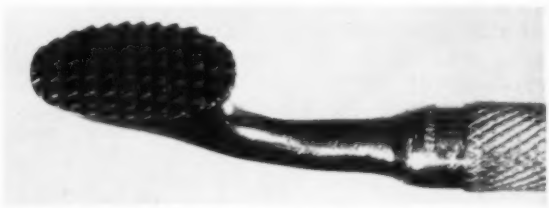


FIG. 228.—The Beck burr, used in the Beck I procedure.

and inferiorly until the base of origin of the left coronary artery can be seen below, and the whole of the inferior surface of the arch of the aorta above.

Attention is then directed to the area of origin of the left coronary artery. The left auricular appendage is grasped with a sponge holder and retracted away from the auriculoventricular groove. The left anterior descending coronary artery is then seen with the great cardiac vein on the surface of the heart in the interventricular area.

A pad of fat obscures its origin from the left common coronary artery and this pad fills in the area between the left anterior sinus of Valsalva and the left posterior flank of the main pulmonary artery. This pad of fat is entered and cleared by sharp dissection; beneath it lies the main left coronary trunk and its point of division. The trunk and its divisions are carefully stripped of connective tissue by sharp dissection and clearly displayed.

It is now possible to see the left main coronary artery from above by retracting the main pulmonary artery to the left.

The great cardiac vein is now ligated at the point where it makes its 90° turn to enter the coronary sinus.

A phenol-dipped pledget is then wiped over the whole stripped and denervated area, and after a period of one minute the phenol is neutralized with absolute alcohol.

The pericardium is then closed with interrupted sutures, and the chest closed in the usual manner.

Results.—We have performed this operation upon 16 dogs. The operative mortality was 4. The first three mortalities were caused by hæmorrhage due to bad operative technique. One dog died in the pound of distemper; 10 came to ligation; 7 survived. Only 1 had a visible infarct.

Thompson.—The chest is entered through a short fifth intercostal space incision placed over the point of maximum impulse. The lung is gently

retracted and a 2-cm. opening is made in the pericardium. Powdered talc 0·5 g. is then placed in the cavity and spread around with the finger. The pericardium is then closed with interrupted sutures and the thorax closed in the usual fashion.

Results.—We have performed this operation on 13 dogs. Operative mortality was 0. Two dogs

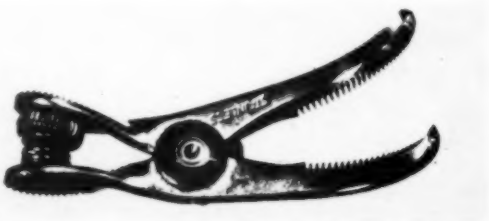


FIG. 229.—Curved, toothed, Pott's-type bulldog clamp used in Beck II procedure.

died in the pound. Eleven were ligated; 5 dogs survived ligation. In those that died infarcts were present over the anterior surface of the left ventricle, and all were large.

Beck II.—With the dog in the prone position, the thorax is entered through the fifth intercostal space, and the lung retracted dorsally and held in place with retraction sutures. The pericardium is opened dorsal to the phrenic nerve. The incision takes an L-shaped course, the base of the L lying just below the auriculoventricular groove as far back as the inferior pulmonary vein, while the other limb lies parallel to the phrenic nerve and extends superiorly to the level of the bifurcation of the pulmonary artery.

The pericardium is held open with retraction sutures and the termination of the coronary sinus displayed. Two sutures of 00000 black silk are passed into the wall of the coronary sinus about 15 mm. from its termination. These sutures are then held up, tenting the sinus wall, and a curved, toothed, Potts-type Bulldog clamp (*Fig.* 229) is applied to the wall of the coronary sinus, partially occluding it. A 5-mm. incision is then made longitudinally into the wall of the sinus, and an end-to-side anastomosis performed between a vein graft from the external jugular and the coronary sinus.

The other end of the vein graft is then anastomosed end-to-side with the descending thoracic aorta, after this has been partially occluded by the Beck clamp (*Fig.* 230) and opened exactly 4·5 mm. with knife and punch (*Fig.* 231).

The type of stitch used varies with individual choice, but a simple running suture is probably the best.

This anastomosis creates an arteriovenous fistula between aorta and right auricle, and a strong thrill is palpable. The pericardium is closed loosely so that there is no external pressure on the graft. The thoracotomy incision is then closed in the usual fashion.

Three weeks later a second thoracotomy is performed through the right fifth intercostal space with the dog in the lateral position. The lung is retracted and the pericardium opened dorsal to the phrenic nerve.

The heart is gently lifted forwards at the apex, and the coronary sinus termination can be seen just anterior to the inferior vena cava. The epicardium is incised and the circumflex branch of the left coronary artery is displayed by dissection with the ball-point dissector (*see Fig.* 227).

A No. 00 atraumatic suture is passed around the coronary sinus 5 mm. from its termination and tied

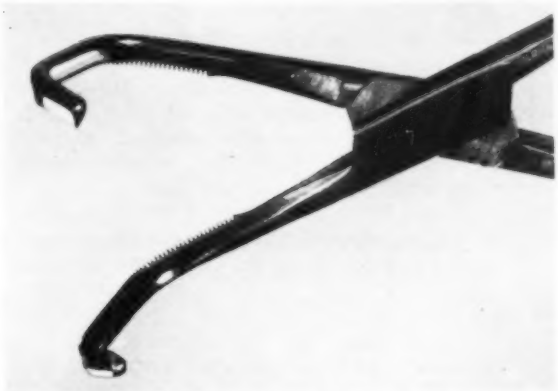


FIG. 230.—Beck clamp used in Beck II procedure.

over a 3-mm. probe. The incision is then closed in the usual manner.

Results.—We have performed this operation upon 23 dogs. This was a difficult procedure to learn and our initial mortality was very high. Eight dogs died on the day of operation from errors in technique, 5 dogs died in the pound after stage II.

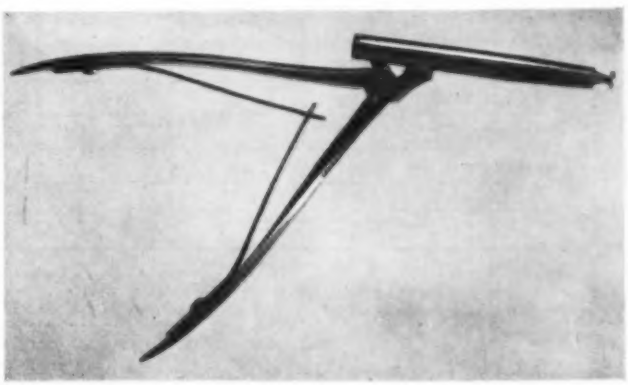


FIG. 231.—Knife and punch used in Beck II procedure.

This group spends longer in the pound than the others because of the multiple stages. Ten dogs were ligated; 7 survived. Only 1 infarct was seen.

This procedure has been discontinued by Beck in the last two years.

With skilful application of the Mauz-Gregg backflow principle, Bakst of Philadelphia has produced objective evidence to show that 'protection' from the operation decreases over a period of six to nine months, and at the end of a year, backflow from the distal end of the divided circumflex artery is no greater with the graft open than when it is occluded. Furthermore, the ligation mortality is nearly the same as that following the less formidable Beck I

procedure. (Bakst, Costas-Durieux, and Bailey, 1955.)

Vineberg.—The thorax is entered through the left fourth intercostal space, and the lung retracted posteriorly and maintained in position by packs held by retraction sutures in the pericardium. The left sternocostalis muscle is removed, and the internal mammary artery gently dissected free.

The pericardium is then opened longitudinally over the left ventricle anterior to the phrenic nerve, and a wide view of the left ventricle obtained.

The internal mammary artery is then freed from its anterior intercostal branches which are tied close to the parent trunk except for the sixth, which is divided 0·5 cm. away. The internal mammary artery is then tied just above the seventh intercostal artery and divided. A shallow tunnel about 2–3 mm. deep and 2 cm. in length is made in the left ventricle with a mosquito clamp, and the mammary artery is gently pulled into the tunnel by traction on the terminal tie. Just before it enters the tunnel the sixth intercostal is cut 1 mm. from the parent trunk. The divided end is affixed to the caudal opening of the tunnel with one 0000 black silk suture. The vessel must lie in such a fashion that no kinking or sharp angulation occurs.

Free bleeding occurs from the open end of the sixth intercostal. Some ooze comes from the proximal end of the ventricular tunnel, but usually it is minimal and may be ignored. If bleeding is profuse the tunnel has been made wrongly and the open ostium badly placed. In this case the operation will almost always fail.

The pericardium is then repaired in such a manner that there is no pressure on the new myocardial artery. The chest is then closed in the usual fashion. The key to the success of this operation has been fully explained by Dr. Vineberg in his article (Vineberg and Buller, 1955).

Results.—We have performed this operation upon 10 dogs. The operative mortality was 0. Ten dogs were ligated; 5 dogs survived. Small infarcts were present in the left ventricle of those that succumbed.

The Combined Operation.—After we had examined our survival tendency we decided to combine a Beck I procedure with the denervation of the left main coronary plexus as in the Fauteux operation.

The first 5 dogs did not survive because of technical errors, but after the initial setback the operative mortality was low, and the ligation mortality encouraging.

Results.—Since standardization of technique we have performed this procedure upon 23 dogs. Operative mortality was 1. Five dogs succumbed to intercurrent disease in the pound. Sixteen dogs were ligated. Twelve dogs survived ligation. Infarcts were present in 3, but were small.

SURVIVAL AND MORTALITY STATISTICS

Beck I Ligations

	Control	Treated			Control	Treated	
Observed number living	2	8	1	Observed number dying	10	4	1
Expected number living	5	5	2	Expected number dying	6·9	6·9	2
Difference	−3	3	3	Difference	3·1	−2·9	3
Difference^2	9	9	4	Difference^2	9·6	8·4	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{9}{5}=1{\cdot}8$	$\frac{9}{5}=1{\cdot}8$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{9{\cdot}6}{6{\cdot}9}=1{\cdot}39$	$\frac{8{\cdot}4}{6{\cdot}9}=1{\cdot}22$	5

Control 12
Treated 12
— 24
Total living 10 41·7 per cent } of 24
Total dying 14 58·3 per cent }

Total cells in line 5 = 6·21
P = less than ·02

Thompson Ligations

	Control	Treated			Control	Treated	
Observed number living	2	5	1	Observed number dying	10	6	1
Expected number living	3·6	3·3	2	Expected number dying	8·4	7·7	2
Difference	−1·6	1·7	3	Difference	1·6	−1·7	3
Difference^2	2·56	2·89	4	Difference^2	2·56	2·89	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{2{\cdot}56}{3{\cdot}6}={\cdot}711$	$\frac{2{\cdot}89}{3{\cdot}3}=87$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{2{\cdot}56}{8{\cdot}4}={\cdot}30$	$\frac{2{\cdot}89}{7{\cdot}7}=3{\cdot}75$	5

Control 12
Treated 11
— 23
Total living 7 30 per cent } of 23
Total dying 15 70 per cent }

Total cells in line 5 = 2·0
n = 1
P is less than ·2

Beck II and Fauteux Ligations

	Control	Treated			Control	Treated	
Observed number living	2	7	1	Observed number dying	10	3	1
Expected number living	4·8	4	2	Expected number dying	7·2	6	2
Difference	−2·8	3	3	Difference	2·8	−3	3
Difference^2	7·8	9	4	Difference^2	7·8	9	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{7·8}{4·8}=1·62$	$\frac{9}{4}=2·25$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{7·8}{7·2}=1·08$	$\frac{9}{6}=1·5$	5

Control 12
Treated 10
— 22
Total living 9 40 per cent } of 22
Total dying 13 60 per cent }

Total cells in line 5 = 6·45
n = 1
P is less than ·02

Vineberg Ligations

	Control	Treated			Control	Treated	
Observed number living	2	5	1	Observed number dying	10	5	1
Expected number living	3·72	3·18	2	Expected number dying	8·17	6·81	2
Difference	−1·72	1·82	3	Difference	1·83	−1·81	3
Difference^2	2·95	3·24	4	Difference^2	3·35	3·28	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{2·95}{3·72}=·793$	$\frac{3·24}{3·18}=1·01$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{3·35}{8·17}=·410$	$\frac{3·28}{6·81}=·482$	5

Control 12
Treated 10
— 22
Total living 7 31·8 per cent } of 22
Total dying 15 68·1 per cent }

Total cells in line 5 = 2·695
n is 1
P is less than ·2

Combined Operation

	Control	Treated			Control	Treated	
Observed number living	2	12	1	Observed number dying	10	4	1
Expected number living	6·0	8·0	2	Expected number dying	6·0	8·0	2
Difference	−0·4	4·0	3	Difference	4·0	−4·0	3
Difference^2	16·0	16·0	4	Difference^2	16·0	16·0	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{16·0}{6·0}=2·67$	$\frac{16·0}{8·0}=2·0$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{16·0}{6·0}=2·67$	$\frac{16·0}{8·0}=2·0$	5

Control 12
Treated 16
— 28
Total living 14 50 per cent } of 28
Total dying 14 50 per cent }

Total cells in line 5 = 9·34
P is less than ·01

Total Ligated

	Control	Treated			Control	Treated	
Observed number living	2	44	1	Observed number dying	10	25	1
Expected number living	6·8	39·3	2	Expected number dying	5·16	29·7	2
Difference	−4·8	4·7	3	Difference	4·84	−4·7	3
Difference^2	23·04	22·09	4	Difference^2	23·4	22·09	4
$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{23·04}{6·8}=3·39$	$\frac{22·09}{39·3}=·56$	5	$\frac{\text{Difference}^2}{\text{Expected number}}$	$\frac{23·4}{5·16}=4·5$	$\frac{22·09}{29·7}=·74$	5

Control 12
Treated 69
— 81
Total living 46 57 per cent } of 81
Total dying 35 43 per cent }

Total cells in line 5 = 9·19
n = 1
P is less than ·01

SUMMARY AND CONCLUSIONS

1. Two hundred and six operations were performed on 113 dogs.

2. In a significant proportion of instances, sufficient protection is given to the myocardium by these procedures to enable it to continue to beat effectively following ligation of the anterior descending coronary artery.

3. The degree of difficulty in the operations upon dogs in our hands has been in the following order: Beck II; Combined; Fauteux; Beck I; Vineberg (*see paragraph* 7); Thompson. The P number over the total series was less than 0·01.

4. The survival following ligation has been :—

Combined, 75 per cent	P less than 0·01
Beck II, 70 per cent	P less than 0·02
Fauteux, 70 per cent	P less than 0·02
Beck I, 66 per cent	P less than 0·02
Thompson, 55 per cent	P less than 0·2
Vineberg, 50 per cent	P less than 0·2
Unprotected, 17 per cent	

5. From these figures and the works of other groups we believe that the Beck I procedure presents the most overall satisfactory immediate and long-term results, and is easy to perform.

6. We are encouraged by our findings in the Combined group.

7. We feel that the Vineberg procedure promises the most likely chance of eventual success, since it shows *microscopically* the growth of 'new' blood-vessels following implantation, and we intend to devote further study to its technique.

8. This work has been the examination of a tendency.

9. A 'chi squared' analysis is included on each operation, and on the whole group of ligated animals. A P-number of 0·02 or less indicates that the results are statistically significant.

REFERENCES

BAKST, A. A., COSTAS-DURIEUX, J., and BAILEY, C. P. (1955), *J. thorac. Surg.*, **30**, 57.

BECK, C. S., and LEIGHNINGER, D. S. (1955), *Ann. Surg.*, **141**, 24.

FAUTEUX, M. (1946), *Ibid.*, **124**, 1041.

LEIGHNINGER, D. S. (1955), *J. thorac. Surg.*, **30**, 397.

THOMPSON, S. A., and PLACHTA, A. (1954), *Ibid.*, **27**, 64.

VINEBERG, A., and BULLER, W. (1955), *Ibid.*, **30**, 411.

SHORT NOTES OF RARE OR OBSCURE CASES

POLYCYSTIC DISEASE OF THE LIVER

By G. R. YARWOOD

DUDLEY ROAD HOSPITAL, BIRMINGHAM

POLYCYSTIC disease of the liver or congenital cystic disease is a rare condition. The liver is the seat of multiple thin-walled cysts containing fluid which is non-parasitic in origin.

Few cases are reported in the British literature, but Davis (1937) in America reviewed 241 recorded cases and Comfort, Gray, Dahlin, and Whitesell (1952) reported on the records of 24 cases. Isolated cases are reported elsewhere.

CASE REPORT

A man, aged 46 years, was referred to Dudley Road Hospital, Birmingham, in November, 1956, on account of persistent attacks of upper abdominal pain. In 1949 he suffered his first attack, which necessitated his admission to hospital as an emergency. At that time no abnormal physical signs were found beyond tenderness in the right hypochondrium. This rapidly disappeared with bed-rest. Investigations were normal.

Since that date he had similar attacks of pain at yearly intervals, all of which settled with bed-rest. Each attack lasted about a week, during which time the pain was continuous both by day and night, and spread over the greater part of the abdomen, being maximal in the right hypochondrium. There was no history of nausea or vomiting and his appetite was normal.

In January, 1956, he suffered from a severe attack. Radiographic examinations of the stomach, duodenum, and gall-bladder were all normal.

In July, 1956, a further attack developed and persisted for several weeks. Accordingly an exploratory laparotomy was advised, to which the patient readily agreed.

ON EXAMINATION.—He was well covered. There was a diffuse tenderness over the whole of the right side of the abdomen. Beyond this no abnormal signs were found.

LABORATORY INVESTIGATIONS.—A radiograph of the chest and an intravenous pyelogram were normal. Liver function tests: Total protein, 5·5 g. per cent; albumen, 3·1 g. per cent. Total globulin, 2·4 g. per cent. Akaline phosphatase, 5·7 K.A. units; thymol turbidity, 2 units; blood-urea, 31 mg. per cent; bilirubin, 0·1 mg. per cent.

AT OPERATION (Nov. 29, 1956).—The abdomen was explored through a right paramedian incision. There was much fat. On palpation of the liver the surface was found to be studded with clusters of small nodules, closely resembling the umbilication of secondary carcinomata. As, however, no intraperitoneal primary could be found and the history was against such a finding the liver was examined. This showed the nodules to be cystic, mostly of small size, varying from ¼ in. to 1–2 in. in diameter. One of these was aspirated and a specimen of the liver taken for section. The kidneys, pancreas, and spleen were all normal.

The patient's post-operative progress was uneventful.

PATHOLOGICAL EXAMINATION.—

Macroscopically.—The piece of liver received measured 2·0 cm. × 2·0 cm. × 2·0 cm., and appeared normal, except for small smooth shiny-walled cysts (average 0·5 cm. diameter) which contained clear colourless fluid.

Microscopically.—One single cyst and a conglomerate group of cysts were all lined by a single layer of thin flattened cells. In the groups of cysts narrow fibrous septa formed the wall between the cysts (*Fig.* 232). At the centre of the group, in a nubbin of fibrous tissue, were several smaller similar cysts and also a few solid cords of

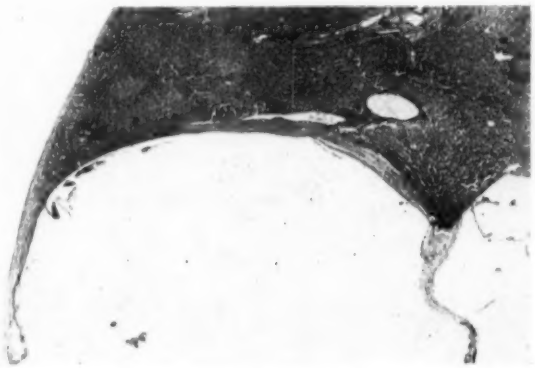


FIG. 232.—Photomicrograph of liver showing cyst wall.

cells and a few groups of similar cells with a central lumen; these resembled the normal bile-ducts of the portal triads. No particular relationship of the cysts to the architecture of the liver was apparent; parenchyma, portal triads, and capsule were each contiguous with the cyst walls.

The cytology and architecture of the liver were normal, apart from a slight increase of lymphocytes in the portal tracts closest to the cysts.

The cysts appeared typical of those of polycystic disease of the liver.

Examination of the aspirated fluid showed it to be sterile, xanthochromic, and containing some red blood-cells. Protein concentration 1500 mg. per cent.

DISCUSSION

Polycystic disease of the liver is said to be more common in females than males. Davis (1937) reporting on a series of 241 cases found the ratio to be 2 : 1. The symptoms usually develop in middle age. It is frequently associated with congenital cystic disease of other organs, notably the kidney, but cysts of the pancreas and spleen may also be present. In the series of 24 cases analysed at the Mayo Clinic there were only 8 in which cystic disease was confined to the liver.

There is considerable discussion as to the origin of the cysts, but the most widely accepted theory is that it is a congenital abnormality of the bile-ducts.

Clinically it may present in a variety of ways :—

1. As a case of hepatomegaly without symptoms.
2. Hepatomegaly with a dragging feeling due to the weight in the upper abdomen.
3. Episodes of severe upper abdominal pain with or without hepatic enlargement.

Laboratory investigations show that the function of the liver is rarely impaired. The diagnosis, therefore, is usually made at operation or autopsy.

Histological examination of the cysts shows them to be lined with a single layer of flattened epithelial cells.

It is natural that treatment is unsatisfactory. Drainage of large cysts may give some temporary relief, but the condition is quite compatible with long life.

SUMMARY

A case of polycystic disease of the liver is described. At exploratory laparotomy its superficial similarity to secondary carcinoma of the liver is noted. The aetiology, symptomatology, and treatment of the condition is discussed.

I wish to thank Mr. K. O. Parsons for his permission to publish this case and Dr. D. J. O'Brien for his histological report.

BIBLIOGRAPHY

COMFORT, M. W., GRAY, H. K., DAHLIN, D. C., and WHITESELL, F. B., jun. (1952), *Gastroenterology*, **20**, 60.

DAVIS, C. R. (1937), *Amer. J. Surg.*, **35**, 590.

ELLIOTT, J. F. (1952), *Canad. med. Ass. J.*, **66**, 164.

NORRIS, R. F., and TYSON, R. M. (1947), *Amer. J. Path.*, **23**, 201.

STOCK, F. E. (1952), *Brit. J. Surg.*, **39**, 530.

SUBMUCOUS LIPOMA OF THE DUODENUM

BY H. L. DUTHIE AND A. P. M. FORREST

UNIVERSITY DEPARTMENT OF SURGERY, WESTERN INFIRMARY, GLASGOW

SUBMUCOUS lipomata of the gastro-intestinal tract are rare and were found in only 309 of 115,251 routine autopsies collected, an incidence of only 0·26 per cent (Weinberg and Feldman, 1955). They consist of aggregations of fat in the submucosa varying from 1 to 6 cm. in diameter, which remain sessile when small, but as their size increases develop a pedicle which may necrose, shedding the fatty tumour into the lumen of the gut.

Weinberg and Feldman could find only 20 examples of submucous lipoma occurring in the duodenum up to 1948, to which they added 6. The majority of all these tumours were incidental findings at post-mortem examination and did not cause symptoms. Only 2 patients with symptoms producing duodenal lipomata were traced in the surgical files of the Mayo Clinic (Smith and Mayo, 1950). Such rarity justifies report of a further case.

CASE REPORT

A 68-year-old woman had been having intermittent attacks of vague lower abdominal colic for two years, with tiredness and loss of weight for six months. Two weeks before her admission to hospital she had developed congestive cardiac failure, for which digitalis had been prescribed. One week later she complained of acute central abdominal pain and nausea, followed by the vomiting of foodstuffs and bile. Despite withdrawal of digitalis the nausea persisted and her doctor noted that

she was tender down the right side of the abdomen. On Aug. 6, 1956, she was admitted to Professor Illingworth's unit for investigation.

On admission she was distressed, cyanosed, and had œdema of the ankles. Her blood-pressure was 170/100. The abdomen was somewhat protuberant and tender on the right side, particularly at the level of the umbilicus, where an ill-defined mass was palpable. A barium enema

FIG. 233.—Appearance of lipoma after opening duodenum.

revealed no abnormality. Barium meal examination showed what appeared to be several filling defects in the second part of the duodenum with possible ulceration, the appearance being suspicious of neoplasm, primarily duodenal.

At laparotomy, the duodenum was enormously dilated from the pylorus to the middle of the third part. On mobilization of the duodenum loop with the head of the pancreas, a polypoidal mass was palpated in the dilated second part at the level of the ampulla. On opening the duodenum this mass prolapsed out through the longitudinal incision, and consisted of a smooth soft lobulated formation of submucous fat covered by normal mucosa (*Fig.* 233). The lipomatous mass (approximately 5 × 3 × 2 cm.) was attached to the duodenal wall by a broad pedicle of at least 2 cm. in diameter, while the surrounding duodenum was generally thickened with greatly swollen plicæ and increased submucosal fat.

A biopsy was taken from the polypoidal mass, the duodenal incision closed, and a posterior gastrojejunostomy performed. Palpation of the gastro-intestinal tract revealed no other abnormality.

Unfortunately the patient died on the third post-operative day as a result of a posterior coronary artery occlusion. Permission for post-mortem examination was not obtained.

COMMENT

The clinical history of vague abdominal colic with a more acute episode of obstructive type and the presence of a palpable tender mass are typical (Smith and Mayo). In the case described the radiological diagnosis of a neoplasm of the duodenum was substantiated at laparotomy. The radiographic picture was similar to that reported by Kirkland and Boyer (1951) in a case of multiple lipomata of the duodenum. The tumour was not sufficiently small to permit transduodenal removal.

SUMMARY

A case of submucous lipoma of the second part of the duodenum, causing symptoms, is described.

REFERENCES

KIRKLAND, W. G., and BOYER, R. A. (1951), *Gastroenterology*, **19**, 42.

SMITH, F. R., and MAYO, C. W. (1950), *Amer. J. Surg.*, **80**, 922.

WEINBERG, T., and FELDMAN, M., sen. (1955), *Amer. J. clin. Path.*, **25**, 272.

INTRAVASCULAR MIGRATION OF HYPODERMIC NEEDLE TO RIGHT LUNG

BY A. M. MACARTHUR

ST. HELIER HOSPITAL, CARSHALTON, SURREY

THE problem of foreign bodies in the cardiovascular system has been fully discussed in Barrett's (1950) comprehensive paper. He mentions the silent migration of foreign bodies and their passage via the venous system and heart into the lung, and refers to a case of his own where such a foreign body, having lodged in the pulmonary artery of the left lower lobe, was followed by a lung abscess seven years later. In the past it has been felt that such foreign bodies should be left alone (Shapiro, 1941), but Barrett suggested that in view of the possibility of late abscess formation their surgical removal should be undertaken. The details of the following case, in which a needle was broken off in the buttock and later migrated to the lung, are thought worth reporting.

CASE REPORT

The patient was a child of 5 suffering from infantile eczema. On Dec. 28, 1954, during an intramuscular injection, a number 12 hypodermic needle was broken off and the fragment retained in the right buttock. A radiograph taken on that day showed the needle lying in the buttock at right angles to the upper end of the femur. Immediately after the accident the child was seen by a surgeon who, in view of the well-known hazards of exploring the buttock for such a foreign body, advised that it should be left alone. The child was seen from time to time after this, and on Jan. 10, 1955, a radiograph taken showed the needle lying anterior to the upper end of the femur and in its long axis (*Fig.* 234). However, a film on March 7 showed the needle to have disappeared and further radiographs located it in the posterior basal segment of the right lower lobe of the lung (*Fig.* 235 A and B).

The migration had been completely symptomless and had presumably taken place via the right femoral vein. The child was admitted to the Brook hospital on March 11,

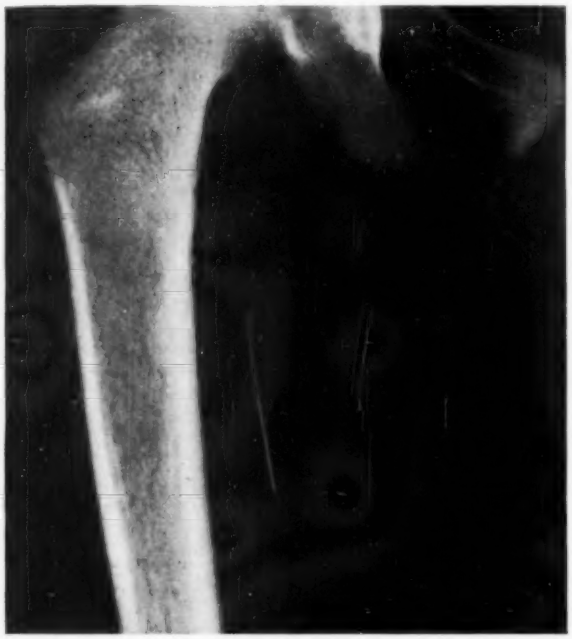
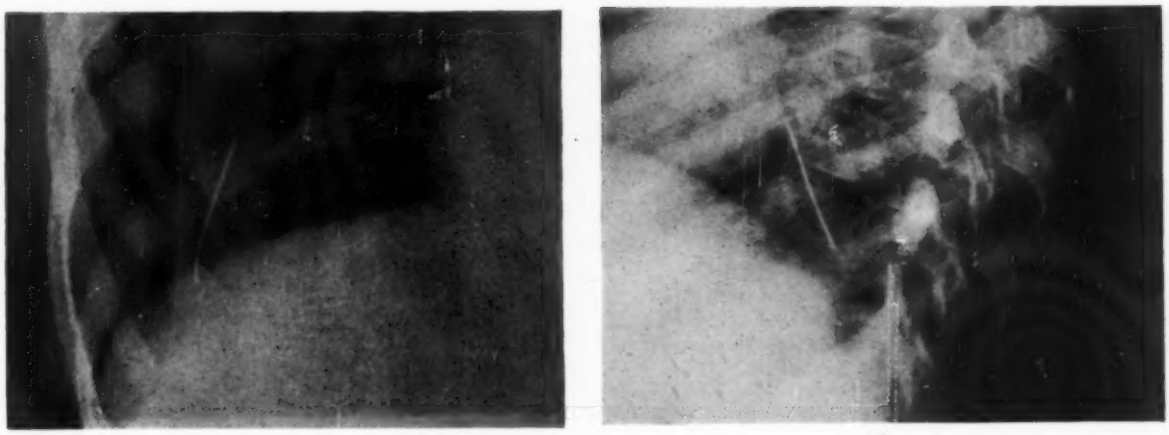


FIG. 234.—Radiograph showing needle lying anterior to femoral shaft and in its long axis.



A B

FIG. 235.—Pre-operative radiographs showing needle lying in posterior basal segment of right lower lobe.

1956, at which time he was in good health with no abnormal physical signs apart from extensive eczema of the face, arms, and legs. Removal of the foreign body was advised because an early operation would entail negligible impairment of pulmonary function, whereas any later intervention designed to deal with a secondary lung abscess would inevitably mean some loss of pulmonary tissue. It was also felt that there was no absolute certainty that the foreign body would remain impacted in its present situation and not undergo retrograde migration back into the heart. Finally, there was considerable pressure from the parents of the child to remove the needle.

On March 14 a right posterolateral thoracotomy was carried out with the patient in the reverse Trendelenburg position. Immediately before the chest was opened a radiograph was taken to ensure that the needle had not moved back up via the main pulmonary trunk into the other lung. The pulmonary artery to the right lower lobe was isolated in the greater fissure and controlled proximally by a thread ligature. By palpation of the atelectatic lower lobe the needle was located in the posterior basal artery and milked down this vessel, until it presented on the diaphragmatic surface of the lung. Through a small incision in the lung parenchyma the peripheral part of this vessel was exposed and the needle pushed through its wall. This small vessel was then ligated and the incision in the lung closed with two catgut sutures. The child made an uninterrupted recovery and was discharged home on the fourteenth post-operative day. When last seen he was in normal health and a radiograph of his chest was within normal limits.

COMMENT

Although a needle lying in the lumen of a small branch of the pulmonary artery may seem harmless, Barrett has stated that " a foreign body lying in the cardiovascular system is always a potential danger to life—wherever it is it should be taken out whenever possible ". In the case reported, early removal was simple, involved negligible loss of pulmonary function, obviated the possibility of late abscess formation, and relieved the child's parents of a considerable burden of anxiety.

REFERENCES

BARRETT, N. R. (1950), *Brit. J. Surg.*, **38**, 416.
SHAPIRO, S. (1941), *Amer. Heart J.*, **22**, 835.

REVIEWS AND NOTICES OF BOOKS

Tumors of the Pituitary Gland and Infundibulum. By JAMES W. KERNAHAN, M.D., Chairman, Sections of Pathologic Anatomy and Surgical Pathology, Mayo Clinic, Rochester, Minnesota; and GEORGE P. SAYRE, M.D., Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota. 10¼ × 7¾ in. Pp. 81, with 67 illustrations. 1956. Washington: Armed Forces Institute of Pathology. $1.00.

THIS is a beautifully illustrated and well-printed atlas published from the Walter Reed Medical Center at Washington, D.C., by two of the well-known pathologists from the staff of the Mayo Clinic. Some plates showing the histology of the tumours are coloured, others are in black and white; all are excellent, as are also the photographs, which have been made at the Mayo Clinic. The text accompanying the illustrations is brief and to the point and well summarizes present knowledge of the pathology of the hypophysis. It is regrettable, however, that throughout the text the term 'adamantinoma', originally introduced because of a fancied but fallacious histological resemblance to paradental tissues, is used for tumours which are better called craniopharyngiomas, suprasellar, or Rathke's pouch cysts, though these and other terms are mentioned as synonyms. The authors have not seen a patient who had a basophilic adenoma which was the cause of Cushing's syndrome, and although they leave the question of the association rather undecided, the inference is that the syndrome, which is certainly produced by adrenal cortical tumours, is probably polyglandular.

The format of this excellent monograph is as attractive as its contents, which makes it a handsome contribution to the atlas of the pathology of tumours being produced by the Institute of Pathology of the U.S. Armed Forces under the auspices of the National Academy of Sciences of the U.S. National Research Council.

Halsted of Johns Hopkins: The Man and his Men. By SAMUEL CROWE. 9 × 6 in. Pp. 247, with numerous illustrations. 1957. Springfield, Ill.: C. C. Thomas. (Oxford: Blackwell Scientific Publications.) 37s. 6d.

As every reader of Cushing's *Life of Osler* will recall, the trustees of Mr. Hopkins' endowment of the University that bears his name were convinced that it was not costly buildings that attracted students, but a distinguished faculty. That had been Newman's idea, too, in the 1850s. The Hopkins trustees were careful to select for their teaching staff men of proven ability who had enjoyed fruitful periods of postgraduate study at the foremost European centres. The "Big Four" of Sargent's well-known portrait—Welch, Osler, Halsted, Kelly—were given on appointment *carte blanche* to choose their own assistants in their respective departments. How well they chose them is evident in this delightful tale of Halsted and his men.

Halsted's figure in this multiple biographical presentation is in every way comparable to that of Billroth in the story of surgery. Dr. Crowe—who unhappily did not live to see his book in print—has here set forth an affectionate pen-portrait of the unique head of a department, in his seemingly casual choice of his assistants, whose work he delighted to encourage and foster. It had been Welch's decision that pathological investigation was to be the guiding spirit of the new school. From the start, Halsted had decided with him that the Department of Surgery was to be a school of surgeons whose training was to be based on a lengthy period of whole-time residence in hospital; his "young men" were to be trained in the gentlest handling of sentient living tissues to discover and practise every technical improvement that would make surgery a safer method of treatment. Halsted's own contributions, it is scarcely too much to claim, had changed the face of American surgery; his first years at Hopkins had been devoted to the experimental study in the laboratory of wound healing: care and gentleness in handling, complete hæmostasis, accurate anatomical suturing with finest silk, the avoidance of tension—all steps based upon the behaviour of the living cells in the wound. These minutiæ, and the use of rubber gloves in operating, are accepted in every surgical theatre to-day: they were not so, however, till Halsted indicated them as the result of his careful experiments in the laboratory. His study of his "young men's" individual capabilities, his pleasure in watching their development, his delight in the joint endeavour of teacher and pupil in solving each surgical problem as it arose, and his generosity in giving them the full share of credit for their individual contribution to each improvement in pathological observation or technical advance, are all set down by one who clearly held his master's memory in affectionate reverence.

In the chapters devoted to "Halsted's men" and their individual accomplishments one can clearly trace the spread of Halsted's teaching and what it has meant to surgical progress in this century: Cushing at Boston; Dandy, Baer, Hugh Young, and Crowe at Hopkins, in company with so many others scattered through other centres. It is an inspiring tale, splendidly told. To Welch, Halsted was "the greatest of America's surgical thinkers", to Leriche, "the surgical heir of Claude Bernard". To all who read this book his figure will remain memorable as one of the creators of scientific surgery.

Year Book of Orthopedics and Traumatic Surgery. 1956–1957. Edited by EDWARD L. COMPERE, M.D., F.A.C.S., F.I.C.S. Professor and Chairman, Department of Orthopedic Surgery, Northwestern University Medical School. 7½ × 5⅛ in. Pp. 336. 208 illustrations. 1957. Chicago: Year Book Publishers. $6.75.

THIS is a useful book, for it surveys all that is new in orthopædics and traumatic surgery. It gives the reader a good précis of modern techniques in orthopædic surgery.

Bone tumours and bone-grafting are particularly well discussed and the concept that heterogenous bone is most useful as a supplement to, not as a substitute for, the autogenous graft is fully set out. In America open surgery for the treatment of fractures is far more often undertaken than in England.

This year book is well illustrated with some excellent clinical pictures and radiographs.

Plastic Arterial Grafts. By W. STERLING EDWARDS, Assistant Professor of Surgery, Medical College of Alabama, Birmingham, Alabama. 9¼ × 6¼ in. Pp. 126 + xii, with 22 illustrations. 1957. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications.) 34s.

PERHAPS no branch of surgery has made such strides as that devoted to cardiovascular surgery. This small monograph has been written for the cardiovascular surgeon, general and thoracic surgeons, and for investigators and research workers in the field of graft replacements. We are living in a traumatic age and more and more arterial injuries are coming under the notice of the surgeon and many of these cases can be treated with arterial grafts.

This book gives an excellent account of the various synthetic fabrics and other artificial substances which have been carefully investigated as to their use for replacement of diseased or damaged arteries. Professor Edwards favours a crimped nylon tubular graft for the following reasons: It is easily sutured; it is permeable to fibroblastic penetration and non-porous enough to allow significant blood-loss; it is flexible yet non-collapsible, so that the tendency to kinking is prevented; it has a low incidence of thrombosis, even in small vessels, and it can be used either as a replacement graft or as a by-pass graft.

An excellent monograph which will be much in demand.

The Metabolic Response to Neonatal Surgery. By PETER PAUL RICKHAM, M.S., D.C.H., F.R.C.S., Consultant Pædiatric Surgeon, Royal Liverpool Children's Hospital, and Alder Hay Children's Hospital, Liverpool. 10½ × 7¾ in. Pp. 93 + x. 1957. Cambridge, Mass.: Harvard University Press. (London: Oxford University Press.) 40s.

NEONATAL surgery has made great progress during the last few years and the mortality of operations performed on young babies has dropped.

This book presents the first careful investigation into the metabolic response to surgery of newborn infants. It describes exceedingly detailed studies and laborious supervision of nine newborn infants undergoing various selected operations. There is an excellent appendix dealing with the various solutions used intravenously and the various milk mixtures used in feeding.

A good and comprehensive bibliography is found at the end of the book.

A most useful reference volume.

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Editors: Sir HENRY TIDY, K.B.E., M.A., D.M., F.R.C.P., and R. MILNES WALKER, M.S., F.R.C.S. Seventy-fifth year. 1957. 8¼ × 5½ in. Pp. 570 + xl. 52 Plates and 46 text illustrations. Bristol: John Wright & Sons, Ltd. 38s. 6d.

THE usefulness to surgeons of the *Medical Annual* increases as the years go by; and to-day the surgical editor provides an excellent survey of surgery in general and its special branches.

The contributors to this 1957 volume are all experts in their own fields and each one has given a pre-eminent review of the literature of the year. The illustrations have been well chosen and have been beautifully reproduced.

No one to-day can keep abreast of the enormous number of periodicals both at home and abroad, and a survey of the important articles is all-important to the clinician; the *Medical Annual* produces this survey in a very practical and pleasant way.

Radiation: What It Is and How It Affects You. By JACK SCHUBERT and RALPH E. LAPP. 8½ × 5¾ in. Pp. 314. 1957. London: Heinemann (Medical Books) Ltd. 18s.

THIS is a popular book written for the laity by two American scientists. It is written in a way that most people will understand and it sets forth the various radiation hazards in a very lucid style. The many and varied problems concerning radiation, such as its nature, how it can be measured, and how it affects the human body, are all set out in an interesting manner. The effects of the explosion of an atom bomb, the symptoms of radiation sickness, and the susceptibility to radiation damage are fully described.

Probably the medical profession in general is not aware of the dangers of exposure to X rays and radium which are ever present in hospitals, and may give rise to latent effects which may appear in future generations. It is a vital question as to whether a pregnant woman should ever be submitted to an X-ray examination of her pelvis because of the effects not only on her ovaries but also on the sex glands of the unborn child.

The more the public read this book the less speculation there will be as to the real radiation hazards.

Medicine and the Navy, 1200-1900. By J. J. KEEVIL, D.S.O. Vol. I. 9 × 6½ in. Pp. 255 + xii. 16 illustrations. 1957. Edinburgh: E. & S. Livingstone Ltd. 40s.

AT last the medical profession has been presented with an excellent work on Medicine and the Navy. The author, a retired Surgeon Commander, saw active service in the Navy during the second world war and was awarded the D.S.O. for his services in an aircraft carrier. The carrier was badly bombed by the Germans in the Mediterranean and Keevil had to deal with several hundred casualties. After the war he retired from the Navy and for several years was librarian at the Royal College of Physicians, where he was in his element delving into ancient medical books. Such is the background of the author of this work and it is quite the right experience to enable him to undertake such a formidable task.

The first volume is divided into three sections; the first dealing with the medieval period, the second with the Tudor period, and the third with the early Stuart period.

The volume is well illustrated with excellent reproductions of early prints. The Barber-Surgeons and their Hall are given quite a place in this book, and rightly so, as the Surgeons and Surgeons' mates had to foregather in the hall for their examination by the Court of the Barber-Surgeons.

Sir Henry Dale writes an introduction to this volume and considers that the work will be of real value to the history of medicine. As Chairman of the Wellcome Trustees Sir Henry has again put himself in the debt of the medical profession by giving a grant for Commander Keevil's research. We look forward to seeing the succeeding volumes with intense interest.

This work should appeal not only to surgeons but to the whole medical profession. It is a classic.

Synopsis of Genitourinary Diseases. By AUSTIN I. DODSON, M.D., F.A.C.S., and J. EDWARD HILL, M.D. 6th edition. 4¾ × 7⅝ in. Pp. 330 with 124 illustrations. 1956. London: Henry Kimpton. 36s. 6d.

DESPITE its recent increase in size this book still remains one which the student can carry in his pocket. It contains a wealth of information in its small compass. The main revision consists in new material on antibiotics and chemotherapy; in a book of this nature the dose of all the substances named should surely be given. The teaching that circumcision should be performed on all newborn male infants prior to their discharge from hospital will not find favour in this country.

Despite these minor faults the teaching is sound and this edition will doubtless be as popular as its predecessors.

British Surgical Practice: Surgical Progress, 1956. Under the General Editorship of Sir ERNEST ROCK CARLING, LL.D., F.F.C.S., F.R.C.P., F.F.R., and Sir JAMES PATERSON ROSS, K.C.V.O., M.S., F.R.C.S., F.A.C.S. 9¾ × 6¾ in. Pp. 396 + vii. 1751 illustrations and 4 Colour Plates. London: Butterworth & Co. 47s. 6d.

WHETHER he owns the original volumes of *British Surgical Practice* or not, every surgeon looks forward to the annual supplement which contains all that is new in surgery. This year the subjects cover a wide field of interest and it would be invidious to pick out particular authors for

praise when all deserve it. The article on Minor Plastic Procedures is both fascinating and clear and makes this form of plastic surgery sound easy.

The recent use of the ileum as a urinary conduit is described in detail and there is a very good article on Parotitis. Amongst the critical surveys is a very good one on Hypothermic Anæsthesia and a very complete one on Partial Nephrectomy, which includes all the original matter and much that is new from the same writer. The " Noter-up " continues to help any author trying to make his article up to date, whilst the abstracts are full enough to tempt him not to read the original articles.

We hope that the publishers will continue to produce this annual volume.

Tumors of the Eye and Adnexa. By ALGERNON B. REESE, M.D., Attending Surgeon and Pathologist, Institute of Ophthalmology, New York City; Clinical Professor of Ophthalmology, College of Physicians and Surgeons, Columbia University. 10¼ × 7¾ in. Pp. 205, with 122 illustrations. 1956. Washington: Armed Forces Institute of Pathology. $2.00.

Tumors of the Eye and Adnexa has been written by Algernon B. Reese for inclusion in the *Atlas of Tumor Pathology*, to be published by the Institute of Pathology of the Armed Forces of the United States.

The epithelial, neuro-ectodermal, and mesodermal tumours are dealt with in a routine manner; the melanomata are given an independent chapter, in keeping with the modern view that these important ocular tumours may arise from more than one germinal layer. The volume is completed by descriptions of tumours of the lacrimal gland and orbit, and of metastatic tumours which may be encountered in the eye, optic nerve, and orbit.

As might be expected by so eminent an authority on ocular pathology, the text of this volume is lucid, authoritative, and informed. As, however, it is destined for an atlas, the illustrations are given pride of place, and these maintain a standard in preparation and reproduction which could hardly be excelled.

This volume will provide a most useful reference to one branch of ocular pathology, and is assured of a warm welcome by those engaged in the ophthalmic specialty.

Transactions of the American Ophthalmological Society. Ninety-second Annual Meeting, Hot Springs, Virginia, 1956. Volume LIV. 9¼ × 6½ in. Pp. 826 + xviii, fully illustrated. 1957. New York: Columbia University Press. (London: Oxford University Press.) 144s.

THE Transactions for the year 1956 cover the academic and clinical side of the specialty over a wide field.

Such a volume does not lend itself to review, but perusal of its diverse contents is a striking testimony to the high standard of contemporary American ophthalmology.

Tumors of the Kidney, Renal Pelvis and Ureter. By BALDWIN LUCKÉ, M.D., Dr. P.H., Late Professor of Pathology, University of Pennsylvania, Philadelphia, U.S.A.; and HANS G. SCHLUMBERGER, M.D., Professor of Pathology, Ohio State University, Columbia, Ohio, U.S.A. Being Sect. VIII, Fasc. 30 of *Atlas of Tumor Pathology*. 10¼ × 7¾ in. Pp. 208, with 187 illustrations. 1956. Washington: Armed Forces Institute of Pathology. $2.25.

MALIGNANT tumours of the kidney account for about 1–2 per cent of cancer of all sites, yet they have produced more confusion in nomenclature than cancer in any other viscus. In this volume the table of contents gives a complete but relatively simple classification of these tumours; it is the best we have seen and does much to clarify the position from the pathological point of view. Indeed the whole work stresses the pathology rather than the clinical side of the disease, yet the latter is not neglected. Emphasis is laid on the variability of the histological picture, and although the effect of the different grades of malignancy on prognosis is mentioned it is not considered so important as it is in this country. The excellent photographic illustrations include examples of almost every known variety of renal tumour. Some of the radiographs, for example *Figs.* 54 and 55, would be of more value if they included a picture of the kidney removed. The text is clearly written and the references are very full, completely correct, and include everything of note.

This is a most valuable addition to the *Atlas* and one which will serve as a standard work of reference for many years.

Surgeon's Journey. The Autobiography of J. Johnston Abraham. 8¼ × 5½ in. Pp. 441 + x, with 23 plates. 1957. London: Heinemann. 25s.

No one can question the truth of Thomas Carlyle's statement that " A well written life is almost as rare as a well spent one "; and it is therefore especially pleasing to be able to draw the prospective reader's attention to a work that reveals both these uncommon attributes. The life of a medical man, and particularly perhaps that of a surgeon, is one full of incident and nearly always provides an entertaining story. The scope of his work, however specialized, brings him in contact with interesting personalities and patients from all walks of life; and there is no subject that has such a wide general appeal as the one related by or relating to a guardian of physical welfare. But it seldom happens that the medical biographer has the added advantage of being also a writer of such compelling charm and practised talent. And still less often does he have the distinction of being a film script-writer! Dr. Johnston Abraham's first book, *The Surgeon's Log*, was published in 1911 and is now in its thirtieth edition. The film *Nora O'Neale*, or *Irish Hearts* as it was entitled in Europe, was based on his novel *The Night Nurse*. In this latest publication he has presented in a most pleasing way the experiences and achievements of a long life devoted to the alleviation of human ills. Chance changed the locale of his activities from time to time, but nothing altered the selfless performance of his life's work. Although he chose to become a surgeon—and never regretted that decision—he always regarded himself " as a physician practising surgery "; and it is his wide knowledge of all branches of medical and surgical science and their historical background that contributes so much to the value and attractiveness of this autobiography.

Essentials of Clinical Proctology. By MANUEL G. SPIESMAN, M.D., L.L.D., F.I.C.P., Associate Professor of Proctology, Chicago Medical School; Chief of Proctology, Mt. Sinai Hospital Rectal Clinics; and LOUIS MALOW, M.D., B.S., F.A.C.S., Associate in Surgery, Chicago Medical School; Proctologist, Grant Hospital. Third edition. 9¼ × 6¼ in. Pp. 316 + viii, with 129 illustrations. 1957. New York and London: Grune & Stratton. $8.75.

THE third edition of this monograph has been completely revised and some new illustrations have been added.

It is a very practical book and the authors' extensive experience in this branch of surgery is evident in the text.

One would have expected a more up-to-date account of ulcerative colitis and its surgical treatment. The statement that cancer only occurs in 1·9 per cent of cases with ulcerative colitis is not in keeping with our ideas in England, where some 10 per cent of cases of ulcerative colitis develop cancer. This complication has made

British surgeons turn to operation; and colectomy carries a very small mortality these days.

However, this monograph only sets out to give the essentials of proctology and therefore it may be said to cover the subject adequately.

Textbook of British Surgery. Edited by Sir HENRY SOUTTAR, C.B.E., D.M. (Oxon.), F.R.C.S., Consulting Surgeon, London Hospital, and J. C. GOLIGHER, Ch.M. (Edin.), F.R.C.S. (Edin. and Eng.), Professor of Surgery, University of Leeds; and Surgeon, Leeds General Infirmary. Volume 2. 10 × 7½ in. Pp. 694 + viii, with 349 illustrations. 1957. London: William Heinemann (Medical Books) Ltd. 105s.

WE welcome the second volume of this important work, for after reading the first volume it made us impatient for its successors. We are not disappointed, for the very high standard of the first volume has been maintained and enhanced by this companion volume.

Lambert Rogers and Charles Langmaid have contributed an excellent account of the surgery of the central nervous system and have illustrated their chapter with some splendid original illustrations.

All the special branches of surgery are well covered by experts in these fields. In particular N. R. Barrett and John Anderson have excelled themselves in their chapter on the surgery of the heart and great vessels.

This work will take its place as the most useful production of surgical knowledge in modern times. It should prove invaluable to postgraduate students who are studying for higher surgical qualifications.

Suprapubic Closure of Vesicovaginal Fistula. By VINCENT J. O'CONOR, B.S., M.D., F.A.C.S., Professor and Head of Department of Urology, Northwestern University Medical School, Chicago, Illinois. 8¾ × 5½ in. Pp. 53 + xii, with 14 illustrations. 1957. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 20s.

THIS monograph describes by means of a short and concise text and clear sketches made from a film the operation used by the author for dealing with the troublesome condition of vesicovaginal fistula. The approach is by a combined transperitoneal and transvesical route, with separation of the bladder from the vagina and wide bisection of the latter to ensure adequate exposure of the fistula.

Dr. O'Conor gives full reports of 29 successful and 2 unsuccessful cases; there were 4 other successes, making 33 in all.

It is a most valuable work and gives an attractive account of an unattractive condition. We can vouch for the success of the method in suitable cases of high fistula.

Martius' Gynecological Operations. Translated and edited by MILTON L. MCCALL, M.D., F.A.C.S., Professor and Head, Departn.ent of Obstetrics and Gynecology, Louisiana State University School of Medicine, New Orleans, and KARL A. BOLTEN, M.D., formerly Instructor, Department of Obstetrics and Gynecology, Louisiana State University School of Medicine, New Orleans. 6¾ × 10⅛ in. Pp. 405 + xiv, with 450 illustrations. London: J. & A. Churchill Ltd. 1957. 155s. net.

THIS is a most useful book written by a German gynæcologist of international repute who has always written from his own mature clinical experience.

This work is profusely illustrated with some 450 well-chosen and original illustrations. It must be said that the great feature of the book is the excellence of the illustrations.

This second English translation is from the seventh edition of Dr. Martius' work and is beautifully reproduced. It may be stated that Dr. Martius has certainly produced a work which is essentially practical with a lucid description of operative technique which will be welcomed by all who have to do with pelvic operations. We would like to congratulate the translators of this book on the able way they have carried out their work.

Surgery: Principles and Practice. By J. GARROTT ALLEN, M.D., Professor of Surgery, University of Chicago; HENRY N. HARKINS, M.D., Ph.D., Professor of Surgery, University of Washington School of Medicine; CARL A. MOYER, M.D., Bixby Professor of Surgery, Washington University School of Medicine, St. Louis; and JONATHAN E. RHOADS, M.D., D.Sc. (Med.), Professor of Surgery, University of Pennsylvania School of Medicine, with 26 contributors. 10¼ × 7 in. Pp. 1495 + xxii, with 623 illustrations. 1957. London: Pitman Medical Publishing Co. Ltd. 110s.

THIS large and comprehensive volume covers the whole field of surgery including gynæcology, orthopædics, and plastic surgery. The editors have enlisted a large number of contributors, who have written on subjects which they have made their own.

The book places strong emphasis on basic knowledge in physiology, anatomy, biochemistry, and pathology. As a reference volume it provides a total picture of surgery in all its departments as practised in America to-day.

It is a pity that in such a work more original drawings have not been incorporated in the text.

Operative Surgery. Edited by CHARLES ROB, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London; and RODNEY SMITH, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Volume 4. 11¼ × 8¾ in. Part VI, Head and Neck and Clearance of Lymph Nodes. Pp. 1–164 + xiv. Part VII, Vascular Surgery. Pp. 1–144. Part VIII, Endocrine Glands. Pp. 1–66. Fully illustrated and indexed. 1957. London: Butterworth & Co. (Publishers) Ltd. 110s.

THE fourth volume of this well-known work is devoted to the operative technique of various operative procedures concerning the head and neck, vascular surgery, and the surgery of the endocrine glands.

As is well known, the main feature of this work is the great number of small illustrations which depict quite clearly the principal steps in the operative technique of the various operations which are in everyday use.

Perhaps the best section in this volume is that devoted to vascular surgery, in which Charles Rob and H. H. G. Eastcott are at their best.

This fourth volume is in keeping with the former ones and the whole work is a real credit to British surgery.

The Treatment of Burns. By CURTIS P. ARTZ, M.D., F.A.C.S., Lt. Col., M.C., U.S.A.(Rtd.). Late Director, Surgical Research Unit, Brooke Army Medical Center, Fort Sam, Houston, Texas; and ERIC REISS, M.D., Instructor in Medicine, Washington University School of Medicine, St. Louis, Missouri. 10 × 6½ in. Pp. 250 + xii, with 105 illustrations. 1957. Philadelphia and London: W. B. Saunders. 52s. 6d.

MUCH has been written regarding the treatment of burns and it may be said that no consensus of opinion is forthcoming. Some surgeons advocate the exposure treatment of burns while others are all for the closed method

with plenty of dressings. This monograph gives the experience gained by the authors in the Brooke Army Medical Center, where over one thousand cases of burns have been treated.

The replacement of body fluids in cases of extensive burns is really the 'sheet anchor' of the modern treatment. All deep burns are skin-grafted and where the periosteum covering a bone is destroyed, the compact bone underlying such an area must be excised.

Perhaps the best chapters in this book are devoted to the repair of facial defects, scar formation, and plastic repair in general. This is an essentially American production with no reference to any British literature. It is a useful guide to the treatment of war burns.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Orthopedic Surgery in the Mediterranean Theater of Operations. By OSCAR P. HAMPTON, Jun., M.D., F.A.C.S., Colonel, M.C., U.S.A.R., Assistant Professor of Clinical Orthopedic Surgery, Washington University School of Medicine, St. Louis, Mo. 10 × 6¾ in. Pp. 368 + xx, with 96 illustrations. 1957. U.S. Printing Office. Office of the Surgeon General, Department of the Army, Washington. $4.00.

Clinical Proctology. By J. PEERMAN NESSELROD, B.S., M.S., M.Sc., M.D., F.A.C.S., F.A.P.S., Assistant Professor of Surgery, Northwestern University Medical School; Attending Surgeon, Division of Proctology, Evanson Hospital, Evanson, Illinois. Second edition. 9½ × 6 in. Pp. 296 + xx, with 72 illustrations. 1957. Philadelphia and London: W. B. Saunders Company Ltd. 49s.

Peripheral Nerve Regeneration. Edited by BARNES WOODHALL, M.D., Professor of Neurosurgery, Duke University Medical School, Durham, North Carolina; and GILBERT W. BEEBE, Ph.D., Statistician, Follow-up Agency Division of Medical Sciences, National Research Council, Washington. 9¼ × 6 in. Pp. 671 + xxiv, with 60 plates. 1957. Washington: Veterans Administration.

The Surgical Management of Pulmonary Tuberculosis. Edited by JOHN D. STEELE, M.D., with a Biographical Sketch of John Alexander, by CAMERON HAIGHT, M.D. 10¼ × 7¼ in. Pp. 213 + xxviii, with numerous illustrations. 1957. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications.) 72s.

Hypophysectomy. Edited by O. H. PEARSON, M.D., F.A.C.P., Associate, Sloan-Kettering Institute, Associate Professor of Medicine, Cornell University Medical College. 8¾ × 5¾ in. Pp. 154 + xii. 1957. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications.) 37s. 6d.

Artificial Limbs in the Rehabilitation of the Disabled. By R. D. LANGDALE KELHAM, O.B.E., F.R.C.S., with 6 collaborators. 9¾ × 6¼ in. Pp. 188 + viii, with 58 illustrations. 1957. London: Her Majesty's Stationery Office. 20s.

Degenerative Changes in the Sternoclavicular and Acromioclavicular Joints in Various Decades. By ANTHONY F. DE PALMA, M.D., James Edward Professor and Head of Department of Orthopedic Surgery, Jefferson Medical College. 9¼ × 6¼ in. Pp. 178 + x, with 105 illustrations. 1957. Springfield, Illinois: Charles C. Thomas. (Oxford: Blackwell Scientific Publications.) 42s.

An Atlas of Cardiac Surgery. Prepared by JORGE A. RODRIGUEZ, M.D., Assistant Professor of Surgical Anatomy and Research Associate, Department of Surgery, University of Mississippi Medical School. 11¾ × 10½ in. Pp. 250 + xii, fully illustrated. 1957. Philadelphia and London: W. B. Saunders Co. 126s.

Cryptorchism. By CHARLES W. CHARNY, M.D., Associate Attending Urologist, Albert Einstein Medical Center, Philadelphia; and WILLIAM WOLGIN, M.D., Assistant Urologist, Albert Einstein Medical Center, Philadelphia. 9½ × 6¼ in. Pp. 140 + x, with 28 illustrations. 1957. London: Cassell and Co. 45s.

Fluid and Electrolytes in Practice. By HARRY STATLAND, M.D., Associate in Medicine, University of Kansas School of Medicine, Consultant in Medicine, Veterans Administration Hospital, Kansas City, U.S.A. Second edition. 9¼ × 6 in. Pp. 229 + xviii, with 31 figures. 1957. London: Pitman Medical Publishing Co. Ltd. 45s.

The Closed Treatment of Common Fractures. By JOHN CHARNLEY, B.Sc., M.B., F.R.C.S., Orthopædic Surgeon, Manchester Royal Infirmary; Orthopædic Surgeon, The Park Hospital, Davyholme; Lecturer in Orthopædics, Manchester University; Late Hunterian Professor, Royal College of Surgeons. 10 × 7 in. Second edition. Pp. 260 + xii, with 199 illustrations. 1957. Edinburgh and London: E. & S. Livingstone Ltd. 50s.

Les Hydrocéphalies du Nourrisson. By C. PHELINE, Chef de Clinique Chirurgicale Infantile; N. BOINEAU, Chef de Clinique Médicale Infantile, Anciens Internes des Hôpitaux d'Alger. 7½ × 5¾ in. Pp. 98, with 13 illustrations. 1957. Paris: Expansion Scientific Française. 950 fr.